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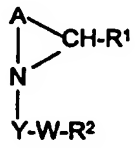

(I)

(57) Abstract

Compounds of formula (I) wherein R^1, Y, W, A and R^2 as defined above are inhibitors of rotamase enzymes in particular FKBP–12 and FKBP–52. The compounds therefore moderate neuronal regeneration and outgrowth and can be used for treating neurological disorders arising from neurodegenerative diseases and nerve damage.

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HETEROCYCLIC COMPOUNDS AS INHIBITORS OF ROTAMASE ENZYMES

This invention relates to 2-heteroaryl-pyrrolidine, -piperidine and -homopiperidine derivatives and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives.

It has been reported that the immunosuppressant FK-506 promotes neurite outgrowth in vitro in neuronal cell line and culture models (see Lyons et al, Pro. Natl. Acad. Sci., 1994, 91, 3191-95 and Snyder et al, Nature Medicine, 1995, 1, 32-37). WO-A-96/40140, WO-A-96/40633 and WO-A-97/16190 disclose compounds that have neurotrophic activity but which lack inhibitory action at the protein phosphatase calcineurin and therefore which have no immunosuppressive activity.

It has been suggested in WO-A-96/40140 and WO-A-96/40633 that the neurotrophic effect of these compounds is mediated, at least in part, by a high affinity interaction with the FK-506 binding proteins, such as FKBP-12, or FKBP-52. However, the mechanism by which this interaction with FKBP- type immunophilins results in a neurotrophic effect is at present unknown. The range of neurotrophic activity that can be realised through this neurotrophic/non-immunosuppressant class of compounds has been explored and it has been found that axon regeneration can be promoted after facial nerve crush and sciatic nerve crush in the rat. It has also been observed that the functional regeneration of dopamine neurons damaged with the toxin MPTP was promoted by the compounds disclosed therein in mice. Additionally, it was reported that restoration of striatal innervation in the rat was promoted by the compounds disclosed therein following 6-hydroxydopamine lesioning of dopaminergic neurons (see Hamilton & Steiner, Current Pharmaceutical Design, 1997, 3, 405-428).

It has now been found that the present compounds are neurotrophic agents which have an affinity for FKBP-type immunophilins. In particular, they are potent inhibitors of the enzyme activity and especially of the cis-trans prolyl

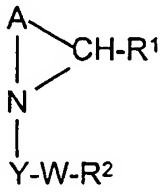
isomerase (rotamase) activity of FKBP-type immunophilins, particularly the immunophilin FKBP-12. The present compounds do not significantly inhibit the protein phosphatase calcineurin and therefore lack any significant immunosuppressive activity.

The present compounds therefore moderate neuronal degeneration and promote neuronal regeneration and outgrowth and can be used for treating neurological disorders arising from neurodegenerative diseases or other disorders involving nerve damage. The neurological disorders that may be treated include senile dementia (Alzheimer's disease) and other dementias, amyotrophic lateral sclerosis and other forms of motor neuron disease, Parkinson's disease, Huntington's disease, neurological deficits associated with stroke, all forms of degenerative disease affecting the central or peripheral nervous system (e.g. cerebellar-brainstem atrophies, syndromes of progressive ataxias), all forms of muscular dystrophy, progressive muscular atrophies, progressive bulbar muscular atrophy, physical or traumatic damage to the central or peripheral nervous system (e.g. spinal cord), herniated, ruptured or prolapsed intervertebrae disc syndromes, cervical spondylosis, plexus disorders, thoracic outlet syndromes, all forms of peripheral neuropathy (both diabetic and non-diabetic), trigeminal neuralgia, glossopharyngeal neuralgia, Bell's Palsy, all forms of auto-immune related disease resulting in damage of the central or peripheral nervous system (e.g. multiple sclerosis, myasthenia gravis, Guillain-Barré syndrome), AIDS related disorders of the nervous system, dapsone ticks, bulbar and retrobulbar affections of the optic nerve (e.g. retinopathies and retrobulbar neuritis), hearing disorders such as tinnitus, and prion diseases.

Preferably, the present compounds can be used for treating senile dementia (Alzheimer's disease) or another dementia, amyotrophic lateral sclerosis or another form of motor neuron disease, Parkinson's disease,

Huntingdon's disease, a neurological deficit associated with stroke, physical or traumatic damage to the central or peripheral nervous system (e.g. spinal cord), a peripheral neuropathy (either diabetic or non-diabetic), multiple sclerosis or a hearing disorder such as tinnitus.

The present invention provides a compound of the formula:



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 is a 5- or 6-membered ring heteroaryl group containing either 1, 2, 3 or 4 nitrogen heteroatoms, or 1 oxygen or sulphur heteroatom and, optionally, 1 or 2 nitrogen heteroatoms, said heteroaryl group being linked to the adjacent carbon atom by a ring carbon atom and optionally substituted by from 1 to 3 substituents each independently selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, -X-(C_3-C_7 cycloalkyl), -X-aryl, -X-het, -X-OH, -X-(C_1-C_4 alkoxy), -X-CO_2R^5, -X-CN, and -X-NR^3R^4;

R^2 is H, phenyl or C_3-C_7 cycloalkyl, said phenyl or cycloalkyl being optionally benzo- or C_3-C_7 cycloalkyl-fused and optionally substituted, including in the benzo- or cycloalkyl-fused portion, by from 1 to 3 substituents each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, -OH, -(C_1-C_6 alkylene)OH, halo and halo(C_1-C_6 alkylene)-,

or R^2 is a 5-, 6- or 7-membered ring heterocyclic group containing either 1, 2, 3 or 4 nitrogen heteroatoms, or 1 oxygen or sulphur heteroatom and, optionally, 1 or 2 nitrogen heteroatoms, said heterocyclic group being saturated or partially or fully unsaturated, optionally benzo-fused and optionally substituted, including

in the benzo-fused portion, by from 1 to 3 substituents each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, halo(C_1-C_6 alkylene)- and -CO_2R^5; said R^2 group being attached to W by any mono- or bicyclic ring carbon atom or heteroatom;

R^3 and R^4 are either each independently selected from H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl and -(C_1-C_6 alkylene)(C_3-C_6 cycloalkyl), or, when taken together, represent unbranched C_3-C_6 alkylene optionally containing O or NR^5;

R^5 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, -(C_1-C_6 alkylene)(C_3-C_6 cycloalkyl) or -(C_1-C_6 alkylene)aryl;

A is unbranched C_3-C_5 alkylene optionally substituted by C_1-C_6 alkyl;

W is a direct link, C_1-C_6 alkylene or C_2-C_6 alkenylene;

X is a direct link, C_1-C_6 alkylene or -(C_0-C_6 alkylene)-Z-(C_0-C_6 alkylene)-;

Y is SO_2, carbonyl, -$CONR^5$-, -CO.CO-, -CH_2CO-, -CS.CO-, -CO.CS- or -CO.CH(OH)-;

Z is O, S, -$CR^5NR^3R^4$-, -$CR^5NR^5(CO_2R^5)$-, -CR^5(aryl^1)-, -NR^5-, -NR^5CO_2-, -$CONR^5$- or -NR^5CO-;

"aryl" is phenyl optionally substituted by from 1 to 3 substituents each independently selected from C_1-C_6 alkyl, -(C_1-C_6 alkylene) OH, C1-C_6 alkoxy, -(C_1-C_6 alkylene)(C_1-C_6 alkoxy), halo, halo(C_1-C_6 alkylene)-, -NR^3R^4, -(C_1-C_6 alkylene)NR^3R^4, -O(C_1-C_6 alkylene)NR^3R^4 and -(C_1-C_6 alkylene)(phthalimido);

"aryl[1] " is phenyl optionally substituted by from 1 to 3 substituents each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, -(C_1-C_6 alkylene)(C_1-C_6 alkoxy), halo and halo(C_1-C_6 alkylene)-; and

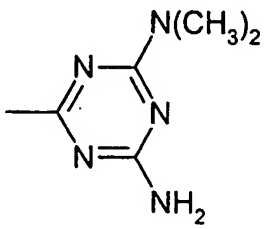
"het" is a 5-, 6- or 7-membered ring heterocyclic group containing either 1, 2, 3 or 4 nitrogen heteroatoms, or 1 oxygen or sulphur heteroatom and, optionally, 1 or 2 nitrogen heteroatoms, said heterocyclic group being saturated or partially or fully unsaturated, or "het" is azetidinyl, said "het" being optionally substituted by from 1 to 3 substituents each independently selected from C_1-C_6 alkyl, -(C_1-C_6 alkylene)(C_3-C_7 cycloalkyl), C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, -(C_1-C_6 alkylene)(C_1-C_6 alkoxy), halo, halo(C_1-C_6 alkylene)-, -NR^3R^4, -CO_2R^5, -(C_1-C_6 alkylene)aryl and -(C_1-C_6 alkylene)NR^3R^4:

with the provisos that

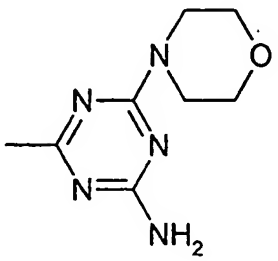
(a) the heteroaryl group of R^1 is not substituted by -(C_0-C_6 alkylene)-Z-(C_0 alkylene)(-OH or -C_1-C_4 alkoxy or -CN or -NR^3R^4) when Z is O, S, -NR^5-, -NR^5CO_2- or -$CONR^5$-; and

(b) when W is a direct link, R^2 is only H when Y is -$CONR^5$- ;

(c) when A is C_3 alkylene, Y is sulphonyl, W is a direct link, and R^2 is para methyl substituted phenyl, then R^1 is not

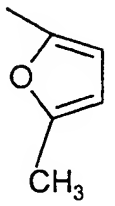


or



;

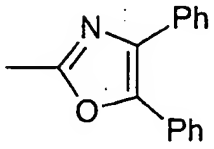
(d) when A is C_4 alkylene, Y is carbonyl, W is C_1 alkylene and R^2 is H, then R^1 is not



;

(e) when A is C_4 alkylene, Y is carbonyl, W is a direct link and R^2 is 3-hydroxy phenyl,

then R^1 is not



,

(f) when A is C_3 alkylene, Y is carbonyl, W is a direct link and R^2 is phenyl, then R^1 is not 2-furyl.

Disclaimers (c) to (f) are based on the following documents: Agr.Biol.Chem. (1971), 35(10), 1572-7; Tetrahedron Lett. (1981), 22(2), 141-4; WO-A-9703973 published 6 February 1997 and Chemical Abstracts, vol. 56, no. 11, abstract no. 13001g.

With the aforementioned disclaimers (c) to (f), the aforementioned compounds for formula (I) are novel. However, if one or more broader disclaimers are required for validity they may be based on the following disclaimers:

(c) wherein when A is C_3 alkylene and Y is sulphonyl, W is a direct link, and R^2 is substituted phenyl, then R^1 is not a diamino substituted triazine (relates to aforementioned disclaimer (c));

(d) wherein Y-W-R^2 does not represent a C_1-C_4 acyl group, when R^1 is an optionally substituted furanyl group (relates to aforementioned disclaimers (d) and (f)); and

(e) wherein R^1 is not an oxazole disubstituted by aryl (relates to aforementioned disclaimer (e)).

Throughout the above definitions, "halo" means fluoro, chloro, bromo or iodo and alkyl, alkoxy, alkenyl, alkylene and alkenylene groups containing the requisite number of carbon atoms, except where indicated, can be unbranched- or branched-chain.

When R^3 and R^4, when taken together, represent unbranched C_3-C_6 alkylene optionally containing O or NR^5, the heteroatom may be positioned either at a terminal position of, or in an intermediate position in, the unbranched C_3-C_6 alkylene group. Examples of such -NR^3R^4 groups include piperazino and morpholino.

The pharmaceutically acceptable salts of the compounds of the formula (I) include the acid addition and the base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate,

p-toluenesulphonate and pamoate salts.

Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts.

For a review on suitable salts see Berge et al, J. Pharm. Sci., 1977, 66, 1-19.

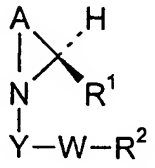
The pharmaceutically acceptable solvates of the compounds of the formula (I) include the hydrates thereof.

Also included within the present scope of the compounds of the formula (I) are polymorphs and radiolabelled derivatives thereof.

A compound of the formula (I) contains one or more asymmetric carbon atoms and therefore exists in two or more stereoisomeric forms. Where a compound of the formula (I) contains an alkenyl or alkenylene group, cis (E) and trans (Z) isomerism may also occur. The present invention includes the individual stereoisomers of the compounds of the formula (I) and, where appropriate, the individual tautomeric forms thereof, together with mixtures thereof.

Separation of diastereoisomers or cis and trans isomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of the formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

Particularly preferred are compounds of the formula (I'):



(I')

wherein R^1, R^2, A, W and Y are as previously defined for a compound of the formula (I).

In the above definitions of a compound of the formula (I) and (I'), the following definitions are preferred.

Preferably, R^1 is triazolyl, isoxazolyl, oxadiazolyl, tetraazolyl, thiazolyl or thiadiazolyl, that is linked to the adjacent carbon atom by a ring carbon atom and optionally substituted by 1, 2 or 3 substituents each independently selected from C_1-C_6 alkyl, -X-aryl, -X-het, -X-CO_2R^5 and -X-NR^3R^4.

More preferably, R^1 is triazolyl, isoxazolyl, oxadiazolyl, tetraazolyl, thiazolyl or thiadiazolyl, that is linked to the adjacent carbon atom by a ring carbon atom and optionally substituted by 1, 2 or 3 substituents each independently selected from C_1-C_6 alkyl, -X-aryl, -X-het, -X-CO_2R^5 and -X-NR^3R^4, wherein

X is a direct link, C_1-C_6 alkylene or -(C_0-C_6 alkylene)-Z-(C_0-C_6 alkylene)-;

Z is O, -$CR^5NR^3R^4$, -$CR^5NR^5(CO_2R^5)$-, -NR^5- or -NR^5CO_2-;

"aryl" is phenyl optionally substituted by from 1 to 3 substituents each independently selected from -(C_1-C_6 alkylene)NR^3R^4, -O-(C_1-C_6 alkylene)NR^3R^4, -(C_1-C_6 alkylene)(phthalimido) and -(C_1-C_6 alkylene) OH;

"het" is piperidyl, pyrazinyl, furyl, piperazinyl, pyrimidinyl or morpholinyl, optionally substituted by from 1 to 3 -(C_1-C_6 alkylene)aryl, -(C_1-C_6 alkylene)(C_3-C_7 cycloalkyl) substituents,

or $-CO_2R^5$ where R^5 is $-(C_1-C_6$ alkylene) aryl or C_1-C_6 alkyl;

or $-(C_1-C_6$ alkylene) NR^3R^4 where "het" is furyl;

R^3 and R^4 are either each independently selected from H and C_1-C_6 alkyl or, when taken together, represent unbranched C_3-C_6 alkylene; and

R^5 is H or C_1-C_6 alkyl.

Yet more preferably, R^1 is 1,2,4-triazolyl, isoxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl or 1,3,4-thiadiazolyl, that is linked to the adjacent carbon atom by a ring carbon atom and optionally substituted by 1, 2 or 3 substituents each independently selected from methyl, benzyl, α-(amino)benzyl, α-(tert-butoxycarbonylamino)benzyl, benzylamino, benzylaminoethyl, aminomethylphenoxymethyl, methylaminomethylphenoxymethyl, dimethylaminomethylphenoxymethyl, pyrrolidinylmethylphenoxymethyl, aminoethoxybenzyl, phthalimidomethylphenoxymethyl, piperidyloxymethyl, benzylpiperidyloxymethyl, benzylpiperidyloxyethyl, morpholinomethyl, benzyloxycarbonylaminoethyl, amino, aminoethyl, R-∝-(amino)benzyl, S-∝-(amino)benzyl, pyrazinyl, benzyloxycarbonylpiperidinyloxymethyl, methylaminofuryl, cyclopropylmethylpiperidyloxymethyl, hydroxymethylphenoxymethyl, tertbutyloxycarbonylpiperazinylethyl, pyrimidinyl, benzylaminomethyl, (S)-α-(benzyloxycarbonylamino)benzyl, piperazinoethyl, phenylcarbonylaminoethyl, dimethylaminomethyl, hydrogen, phenyl, cyclohexylamino or (R)-α-(benzyloxycarbonylamino)benzyl.

More preferably still, R^1 is

5-benzyl-1,2,4-oxadiazol-3-yl,

5-(4-[phthalimidomethyl]phenoxymethyl)-1,2,4-oxadiazol-3-yl,

5-(4-aminomethylphenoxymethyl)-1,2,4-oxadiazol-3-yl,

5-(4-dimethylaminomethylphenoxymethyl)-1,2,4-oxadiazol-3-yl,

5-(4-pyrrolidinomethylphenoxymethyl)-1,2,4-oxadiazol-3-yl,
5-(4-methylaminomethylphenoxymethyl)-1,2,4-oxadiazol-3-yl,
5-(1-benzylpiperid-4-yloxymethyl)-1,2,4-oxadiazol-3-yl,
5-(α-[tert-butoxycarbonylamino]benzyl)-1,2,4-oxadiazol-3-yl,
5-morpholinomethyl-1,2,4-oxadiazol-3-yl,
5-(2-[1-benzylpiperid-4-yloxy]ethyl)-1,2,4-oxadiazol-3-yl,
5-(1H-piperid-4-yloxymethyl)-1,2,4-oxadiazol-3-yl,
5-[α-[amino]benzyl)-1,2,4-oxadiazol-3-yl,
5-(2-[benzyloxycarbonylamino]ethyl)-1,2,4-oxadiazol-3-yl,
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5-(2-[benzylamino]ethyl)-1,2,4-oxadiazol-3-yl,
5-(4-[2-aminoethoxy]benzyl)-1,2,4-oxadiazol-3-yl,
5-methyl-1,3,4-thiadiazol-2-yl,
1H-1,2,4-triazol-3-yl,
1-benzyl-1H-1,2,4-triazol-3-yl,
5-benzyl-4-methyl-4H-1,2,4-triazol-3-yl,
5-amino-1,3,4-oxadiazol-2-yl,
5-benzylamino-1,3,4-oxadiazol-2-yl,
3-methylisoxazol-5-yl,
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5-(1-benzyloxycarbonylpiperid-4-yloxymethyl)-1,2,4-oxadiazol-3-yl,
5-(1-cyclopropylmethylpiperid-4-yloxymethyl) -1,2,4-oxadiazol-3-yl,
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5-[2-(4-tert-butoxycarbonylpiperazin-4-yl)ethyl] -1,2,4-oxadiazol-3-yl,
5-(pyrimidin-2-yl) -1,2,4-oxadiazol-3-yl,

5-methyl-1,2,4-oxadiazol-3-yl,
5-benzylaminomethyl-1,2,4-oxadiazol-3-yl,
5-(S)-(α-[benzyloxycarbonylamino]benzyl) -1,2,4-oxadiazol-3-yl,
5-(R)-(α-[benzyloxycarbonylamino]benzyl) -1,2,4-oxadiazol-3-yl,
5-[2-(4H-piperazin-1-yl)ethyl] -1,2,4-oxadiazol-3-yl,
5-[2-(phenylcarbonylamino)ethyl] -1,2,4-oxadiazol-3-yl,
5-[2-(dimethylamino)ethyl] -1,2,4-oxadiazol-3-yl,
1,2,4-oxadiazol-3-yl,
5-phenyl -1,2,4-oxadiazol-3-yl,
2-benzyl-2H -1,2,3,4-tetraazol-5-yl,
5-benzyl-1,3,4-oxadiazol-2-yl,
5-[2-(phenyl)ethyl] -1,3,4-oxadiazol-2-yl,
5-methyl-2H-1,2,3,4-tetraazol-5-yl,
5-cyclohexylamino -1,3,4-oxadiazol-2-yl,
5-methyl -1,3,4-oxadiazol-2-yl,
3-methyl -1,2,4-oxadiazol-3-yl,
5-methyl -1,3-thiazol-2-yl,
5-methyl-1H- 1,2,4-triazol-3-yl,
5-aminomethyl -1,2,4-oxadiazol-3-yl or
2H- 1,2,3,4-tetraazol-5-yl.

Most preferably R^1 is
5-benzyl-1,2,4-oxadiazol-3-yl,
5-(4-[phthalimidomethyl]phenoxymethyl)-1,2,4-oxadiazol-3-yl,
5-(4-aminomethylphenoxymethyl)-1,2,4-oxadiazol-3-yl,
5-(4-dimethylaminomethylphenoxymethyl)-1,2,4-oxadiazol-3-yl,
5-(4-pyrrolidinomethylphenoxymethyl)-1,2,4-oxadiazol-3-yl,
5-(4-methylaminomethylphenoxymethyl)-1,2,4-oxadiazol-3-yl,

5-(1-benzylpiperid-4-yloxymethyl)-1,2,4-oxadiazol-3-yl,
5-(α-[tert-butoxycarbonylamino]benzyl)-1,2,4-oxadiazol-3-yl,
5-(2-[1-benzylpiperid-4-yloxy]ethyl)-1,2,4-oxadiazol-3-yl,
5-(1H-piperid-4-yloxymethyl)-1,2,4-oxadiazol-3-yl,
5-[α-[amino]benzyl)-1,2,4-oxadiazol-3-yl,
5-(2-[benzylamino]ethyl)-1,2,4-oxadiazol-3-yl,
5-(4-[2-aminoethoxy]benzyl)-1,2,4-oxadiazol-3-yl,
5-(pyrazin-2-yl)-1,2,4-oxodiazol-3-yl,
5-(R)-[α-(amino)benzyl]-1,2,4-oxadiazol-3-yl,
5-(S)-[α-(amino)benzyl]-1,2,4-oxadiazol-3-yl,
5-(5-methylaminofuran-2-yl)-1,2,4-oxadiazol-3-yl,
5-(1-benzyloxycarbonylpiperid-4-yloxymethyl)-1,2,4-oxadiazol-3-yl,
5-(1-cyclopropylmethylpiperid-4-yloxymethyl) -1,2,4-oxadiazol-3-yl,
5-(4-hydroxymethylphenoxymethyl) -1,2,4-oxadiazol-3-yl,
5-[2-(4-tert-butoxycarbonylpiperazin-4-yl)ethyl] -1,2,4-oxadiazol-3-yl,
5-(pyrimidin-2-yl) -1,2,4-oxadiazol-3-yl,
5-benzylaminomethyl-1,2,4-oxadiazol-3-yl,
5-(S)-(α-[benzyloxycarbonylamino]benzyl) -1,2,4-oxadiazol-3-yl or
5-[2-(4H-piperazin-1-yl)ethyl] -1,2,4-oxadiazol-3-yl.

Preferably, R^2 is H, phenyl or C_3-C_7 cycloalkyl, said phenyl or cycloalkyl being optionally substituted by from 1 to 3 halo substituents, or R^2 is a 5- or 6- membered ring heterocyclic group containing either 1 or 2 nitrogen heteroatoms or 1 oxygen heteroatom, said heterocyclic group being saturated or partially or fully unsaturated, optionally benzo-fused and optionally substituted, including in the benzo-fused portion, by from 1 to 3 C_1-C_6 alkyl, arylalkoxycarbonyl (e.g. benzyloxycarbonyl), halo or halo (C_1-C_6) alkyl, substituents,

said R^2 group being attached to W by any mono- or bicyclic ring carbon atom or heteroatom.

More preferably, R^2 is H, phenyl, cyclopentyl, cyclohexyl or cycloheptyl, said phenyl being optionally substituted by from 1 to 3 fluoro substituents, or R^2 is imidazoly, pyrrolidinyl, piperidinyl or tetrahydrofuranyl, said imidazolyl or tetrahydrofuranyl group being optionally benzo-fused and optionally substituted, including in the benzo-fused portion, by from by from 1 to 3 methyl or bromine or fluorine substituents,

said R^2 group being attached to W by any mono- or bicyclic ring carbon atom.

Yet more preferably, R^2 is H, fluorophenyl, cyclohexyl, methylimidazolyl, benzimidazolyl, furanyl, cyclopentyl, cycloheptyl, bromobenzimidazolyl or fluorobenzimidazoyl.

Most preferably, R^2 is H, 4-fluorophenyl, cyclohexyl, 1-methyl-1H-imidazol-4-yl, 1H-benzo[d]imidazol-2-yl, tetrahydrofuran-3-yl, cyclopentyl, cycloheptyl or 5-bromo-1H-benzo[d]imidazol-2-yl.

Preferably, W is a direct link or C_1-C_6 alkylene.

More preferably, W is a direct link, methylene, ethylene or 2,2-dimethyl-1,3-propylene. Most preferably, W is a direct link or methylene.

Preferably, Y is SO_2 or -$CONR^5$-.

Most preferably, Y is SO_2 or -CONH-.

Preferred examples of -Y-W-R^2 include:

5-bromo1H-benzo[d]imidazol-2-yl sulphonyl,
1H-benzo[d]imidazol-2-ylsulphonyl,
1-methyl-1H-imidazol-4-ylsulphonyl,
tetrahydrofuran-3-ylmethylsulphonyl,
cyclohexylmethylsulphonyl,
4-fluorophenylsulphonyl,
N-(2,2-dimethylprop-1-yl)aminocarbonyl,
cyclopentylmethyl sulphonyl,
cycloheptylmethyl sulphonyl,
1-(benzyloxycarbonyl)pyrrolidin-3-ylmethylsulphonyl,
1-(benzyloxycarbonyl)piperid-3-ylmethylsulphonyl,
benzylaminocarbonyl or
phenethylaminocarbonyl.

Highly preferred examples of -Y-W-R^2 include:
5-bromo1H-benzo[d]imidazol-2-yl sulphonyl,
1H-benzo[d]imidazol-2-ylsulphonyl,
cyclohexylmethylsulphonyl,
4-fluorophenylsulphonyl,
cyclopentylmethyl sulphonyl or
cycloheptylmethyl sulphonyl.

Preferably, A is unbranched C_3-C_4 alkylene (i.e. 1,3-propylene or 1,4-butylene). Most preferably A is C_4 alkylene.

In a preferred embodiment of the present invention R^1 is 1,2,4 or 1,3,4 oxadiazole, that is linked to the adjacent carbon atom by a ring carbon

atom which is optionally preferably-mono-substituted by one of -X-aryl or -X-het wherein X is preferably selected from -(C_0-C_2 alkylene)-Z-(C_0-C_2 alkylene), more preferably -(C_1 alkylene)-Z-(C_0 alkylene) where Z is -O-; or X is a direct link or -(C_1-C_2 alkylene); or X is -(C_0 alkylene)-Z-(C_0 alkylene) where Z is -$CR^5NR^3R^4$, or -CR^5 NR^5 (CO_2R^5) where R^3 and R^4 are selected from H,-(C_1-C_3 alkylene), more preferably H,-(C_1-C_2 alkylene) and R^5 is H or -(C_1-C_4 alkylene), or -(C_1-C_2 alkylene)aryl; or X is -(C_1-C_2 alkylene) -Z-(C_1-C_2 alkylene)(aryl) where Z is NR^5 and R^5 is H or -(C_1-C_2 alkylene)-;

wherein aryl of -X-aryl is phenyl optionally substituted by from 1 to 3 susbtituents independently selected from -(C_1-C_3 alkylene) NR^3 R^4, -(C_1-C_6 alkylene)(phthalimido); -O(C_1-C_3 alkylene) NR^3 R^4 or -CO_2R^5 wherein R^3 and R^4 are each independently selected from H, C_1-C_3 alkyl or, when taken together, represent unbranched C_3-C_5 alkylene; and R^5 is H, C_1-C_4 alkyl or -(C_1-C_2 alkylene) aryl;

wherein "het" of -X-het is piperidinyl, furyl, pyrazinyl, pyrimidinyl or piperazinyl optionally substituted by -(C_1-C_3 alkylene)(-C_3-C_6 cycloalkyl), -$C0_2R^5$, -(C_1-C_3 alkylene)NR_3R_4 or -(C_1-C_2 alkylene)aryl wherein aryl is phenyl and wherein R^3 and R^4 are selected from H,-(C_1-C_3 alkylene), more preferably H,-(C_1-C_2 alkylene) and R^5 is H or -(C_1-C_4 alkylene), or -(C_1-C_2 alkylene)aryl;

or X is -(C_1-C_2 alkylene) -Z-(C_1-C_2 alkylene)(aryl) where Z is NR^5 and R^5 is H or -(C_1-C_2 alkylene)-.

Further preferred embodiments of the present invention are as follows:

1*H*-Benzo[d]imidzol-2-yl[2S]-2-(5-benzyl-1,2,4-oxadiazol-3-yl)-1-piperidylsulphone, 2-[4-(3-[(2*S*)-1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)piperidyl]-1,2,4-oxadiazol- 5-ylmethoxy)benzyl]-1,3-isoindolinedione, 4-(3-[(2*S*)-1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5- ylmethoxy)benzylamine, *N*-[4-(3-[(2*S*)-1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzyl]-*N*,*N*-dimethylamine, 3-[1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-5-[4-(1- pyrrolidylmethyl)phenoxy]methyl-1,2,4-oxadiazole, *N*-[4-(3-[1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzyl]-*N*-methylamine, 4-[3-((2S)-1-[Cyclohexylmethylsulfonyl]-2-piperidyl)-1,2,4-oxadiazol-5-ylmethoxy]benzylamine, 5-[(1-Benzyl-4-piperidyl)oxymethyl]-3-[(2*S*)-1-cyclohexylmethylsulfonyl-2-piperidyl]-1,2,4-oxadiazole, 3-[(2*S*)-1-Cyclohexylmethylsulfonyl-2-piperidyl]-5-[4-piperidyloxymethyl]-1,2,4-oxadiazole, (3-[(2*S*)-1-Cyclohexylmethylsulfonyl-2-piperidyl]-1,2,4-oxadiazol-5-yl)(phenyl)methylamine, 5-(3-(2*S*)-1-[(Cyclohexylmethyl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)-2-furyl]methylamine, *N*-(2-(3-[1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-yl)ethyl)benzylamine, 2-[4-(3-[1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethyl)phenoxy]ethylamine, *N*-(3-[1-(1*H*-benzo[d]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethyl)-*N*-benzylamine, 2-[(2*S*)-2-5-[(4-Piperidyloxy)methyl]-1,2,4-oxadiazol-3-yl-1-piperidyl]sulfonyl-1*H*-benzo[d]imidazole, 2-[(2*S*)-2-[5-([1-(Cyclopropylmethyl)-4-piperidyl]oxymethyl)-1,2,4-oxadiazol-3-yl]-1-piperidyl]sulfonyl-1*H*-benzo[d]imidazole, 2-[(2*S*)-2-(5-Benzyl-1,2,4-oxadiazol-3-yl)-1-piperidyl]sulfonyl-5-bromo-1*H*- benzo[d]imidazole, 2-4-[(3-(2*S*)-1-[(5-Bromo-1*H*-benzo[d]imidazol-2-yl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)methoxy]benzyl-1,3-isoindolinedione,

4-[(3-(2*S*)-1-[(5-Bromo-1*H*-benzo[d]imidazol-2-yl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)methoxy]benzylamine, *tert*-Butyl 4-[2-(3-(1*S*)-2-[(cyclohexylmethyl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)ethyl]-1-piperazinecarboxylate, (*R*)-(3-{(2*S*)-1-[(Cyclohexylmethyl)sulfonyl]-2-piperidyl}-1,2,4-oxadiazol-5-yl)(phenyl)methylamine, (*S*)-(3-{(2*S*)-1-[(Cyclohexylmethyl)sulfonyl]-2-piperidyl}-1,2,4-oxadiazol-5-yl)(phenyl)methylamine, 2-({2-[5-(2-pyrimidinyl)-1,2,4-oxadiazol-3-yl]-2-piperidyl}sulfonyl)-1*H*- benzo[d]imidazole, Benzyl 4-(3-[(2*S*)-1-(1*H*-benzo[d]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4- oxadiazol-5-ylmethoxy)-1-piperidinecarboxylate, (2S)-2-(5-Benzyl-1,2,4-oxadiazol-3-yl)-1-[(cyclopentylmethyl)sulphonyl]piperidine, (2S)-2-(5-Benzyl-1,2,4-oxadiazol-3-yl)-1- [(cyclohexylmethyl)sulphonyl]piperidine, (2S)-2-(5-Benzyl-1,2,4-oxadiazol-3-yl)-1-[(cycloheptylmethyl)sulphonyl]piperidine, tert-Butyl-N-(3-{(2S)-1-(cyclohexylmethyl)sulphonyl-2-piperidyl}-1,2,4-oxadiazol 5-yl)(phenyl)methylcarbamate, (2S)-2-(5-{2-[(1-Benzyl-4-piperidyl)oxy]ethyl}-1,2,4-oxadiazol-3-yl)-1-(cyclohexylmethyl)sulphonyl]piperidine, {4-{3-{2S-1-[4-Fluorophenyl)sulphonyl]piperidyl}-1,2,4-oxadiazol-5-yl)methoxy]phenyll}methanol, 2-(3-{(2S)-1-[4-Fluorophenyl)sulphonyl]piperidyl}-1,2,4-oxadiazol-5-yl)pyrazine or 1-[2-(3-(1S)-2-[(Cyclohexylmethyl)sulphonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)ethyl]piperazine.

According to a further aspect of the invention there are provided compounds of formula (I) as defined herein before but wherein the optional substituent on R^2, where R^2 is a 5-, 6-, or 7-membered ring heterocyclic group, is not, CO_2R^5; or wherein the optional substituent on the "aryl" group of -X-aryl or R^5 is not -(C_1-C_6 alkylene)OH; or wherein the

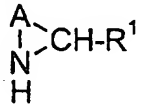
optional substituent on the -X-het group is not C_3-C_7 cycloalkyl or -(C_1-C_6 alkylene)(C_3-C_7 cycloalkyl).

Particularly preferred examples of the compounds of the formula (I) are as described in the Examples section hereafter.

The compounds of the formula (I) can be prepared using conventional procedures such as by the following illustrative methods.

1. All the compounds of the formula (I) can be prepared by

(a) reaction of a compound of the formula:



(II)

wherein R^1 and A are as previously defined for a compound of the formula (I), with a compound of the formula:

$$L^1\text{-}Y\text{-}W\text{-}R^2 \qquad (III)$$

wherein R^2, W and Y are as previously defined for a compound of the formula (I) and L^1 is a suitable leaving group, e.g. fluoro, chloro or bromo; or

(b) by ring formation or ring closure of a corresponding open ring structure, to formula (II), wherein the said open ring corresponds to an optionally substituted heterocycle R^1 followed by reaction with a compound of formula (III) as detailed herein before; or

(c) by ring formation or ring closure of a corresponding open ring structure, to formula (I), wherein the said open ring corresponds to an optionally substituted heterocycle R^1 .

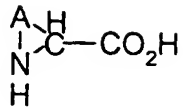
If an acid addition salt of a compound of the formula (II) is used as the starting material, this may be converted to the free base in situ using a suitable acid acceptor, e.g. ethyldiisopropylamine.

For all definitions of Y, L^1 may be chloro and the reaction can be carried out in the presence of a suitable additional acid acceptor, e.g. ethyldiisopropylamine or triethylamine, and in a suitable solvent, e.g. dichloromethane. Where Y is SO_2, L^1 may be fluoro and the reaction can be carried out under similar conditions.

Where Y is carbonyl, $-CONR^5-$, -CO.CO-, -CO.CS- or -CO.CH(OH)-, L^1 may also be a group that forms an activated derivative of a carboxylic acid, e.g. an activated ester or imidazol-1-yl. The reaction may be carried out under conventional conditions.

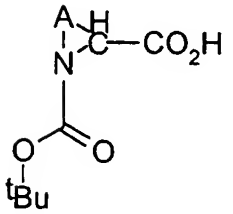
The intermediate compounds of the formula (II) may be prepared by conventional methods, for example, where the heteroaryl group of R^1 is a 1,2,4-oxadiazol-3-yl group, by the route shown in Scheme 1.

Scheme 1



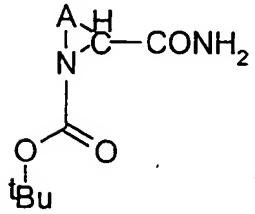
(IV)

Carbamate formation
(e.g. di-t-butyldicarbonate, aqueous sodium hydroxide, 1,4-dioxane)



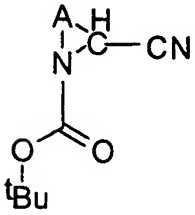
(V)

Amide formation (e.g. ethyl chloroformate, aqueous ammonia, triethylamine, tetrahydrofuran)



(VI)

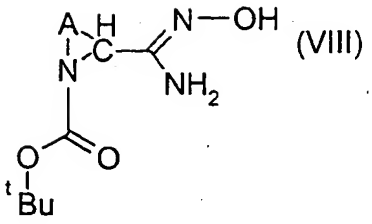
Dehydration
(e.g. oxalyl chloride, dimethylformamide, pyridine, acetonitrile)



(VII)

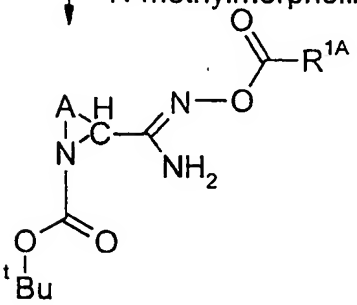
Hydroxyamidine formation (e.g. hydroxylamine hydrochloride, aqueous sodium carbonate, methanol)

Scheme 1 Contd./



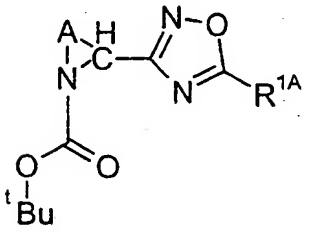
(VIII)

Coupling (e.g. HO_2C-R^{1A}, hydroxybenzotriazole, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 4-dimethylaminopyridine, N-methylmorpholine, dichloromethane)



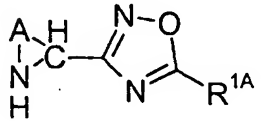
(IX)

Ring closure (e.g. xylene, heat)



(X)

Deprotection (e.g. hydrogen chloride, dichloromethane)



.HCl (IIA)

wherein A is as previously defined for a compound of the formula (I) and R^{1A} is a relevant group corresponding to an optional substituent on the heteroaryl group as previously defined for R^1 for a compound of the formula (I).

A salt of the formula (IIA) is usually used directly in the reaction with a compound of the formula (III) where it may be converted to the corresponding free base of the formula (II) in situ using a suitable acid acceptor, e.g. ethyldiisopropylamine.

The intermediate compounds of the formula (III) may be prepared by conventional methods.

2. The compounds of the formula (I) wherein Y is -CONH- and R^1, R^2, A and W are as previously defined for a compound of the formula (I) can be prepared by reaction of a compound of the formula (II) wherein R^1 and A are as previously defined for a compound of the formula (I), with an isocyanate of the formula:

$$R^2\text{-W-NCO} \qquad \text{(XI)}$$

wherein R^2 and W are as previously defined for a compound of the formula (I).

The reaction may be carried out in a suitable solvent, e.g. dichloromethane.

The intermediate compounds of the formula (XI) can be prepared by conventional methods.

3. The compounds of the formula (I) wherein Y is -CONR^5- and R^1, R^2, R^5, A and W are as previously defined for a compound of the formula (I) can be prepared by reaction of a compound of the formula (II) wherein R^1 and A are as previously defined for a compound of the formula (I), first with a suitable carbonylation reagent, e.g. phosgene [or an equivalent thereof (e.g. triphosgene)] or 1,1'-carbonyldiimidazole, and then with a compound of the formula:

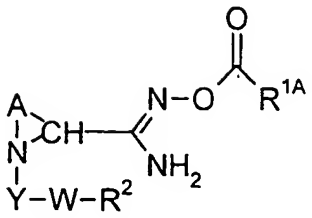
$$R^2\text{-}W\text{-}NHR^5 \qquad (XII)$$

wherein R^2, R^5 and W are as previously defined for a compound of the formula (I), the reaction being optionally carried out in the presence of a suitable acid acceptor, e.g. triethylamine.

The reaction may be carried out in a suitable solvent, e.g. dichloromethane.

The intermediate amines of the formula (XII) can be prepared by conventional methods.

4. The compounds of the formula (I) wherein R^1 is an optionally substituted 1,2,4-oxadiazol-3-yl heteroaryl group and R^2, A, W and Y are as previously defined for a compound of the formula (I) can be prepared by ring closure of a compound of the formula:

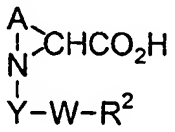


(XIIA)

wherein R^2, A, W and Y are as previously defined for a compound of the formula (I) and R^{1A} is a relevant group corresponding to an optional substituent on the heteroaryl group as previously defined for R^1 for a compound of the formula (I).

The reaction may be carried out in a suitable solvent, e.g. xylene or pyridine, and at the reflux temperature thereof.

The intermediate compounds of the formula (XIIA) can be prepared by a similar method to that used to prepare a compound of the formula (IX) in Scheme 1 by initially converting a compound of the formula (IV) to a compound of the formula:

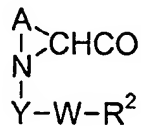


(XIII)

wherein R^2, A, W and Y are as previously defined for a compound of the formula (I), using a conventional method, and then by following the route indicated therein.

5. The compounds of the formula (I) wherein R^1 is an optionally substituted 1,3,4-oxadiazolyl heteroaryl group and R^2, A, W and Y are as previously

6. defined for a compound of the formula (I) can be prepared by ring closure of a compound of the formula:



(XIV)

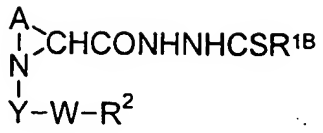
wherein R^2, A, W and Y are as previously defined for a compound of the formula (I) and R^{1A} is a relevant group corresponding to an optional substituent on the heteroaryl group as previously defined for R^1 for a compound of the formula (I).

The reaction may be carried out under suitable conditions such as using a mixture of triphenylphosphine, iodine and triethylamine in dichloromethane. A compound of the formula (XIV) can be prepared by reaction of a compound of the formula (XIII) with a compound of the formula:

$$R^{1A}\ CONHNH_2 \qquad (XV)$$

under conventional dehydration conditions.

6. The compounds of the formula (I) wherein R^1 is a 1,3,4-oxadiazolyl heteroaryl group bearing an optionally substituted amino substituent (R^{1B}) (as previously defined for R^1) and R^2, A, W and Y are as previously defined for a compound of the formula (I) can be prepared by ring closure of a compound of the formula:



(XVI)

wherein R^2, A, W and Y are as previously defined for a compound of the formula (I) and R^{1B} is a relevant optionally substituted amino substituent as defined above.

The reaction may be carried out using mercuric oxide in 1,4-dioxane and at the reflux temperature.

A compound of the formula (XVI) can be prepared by reaction of a compound of the formula (XIII) first with a carboxyl group activating reagent (e.g. 1,1'-carbonyldiimidazole) followed by a compound of the formula:

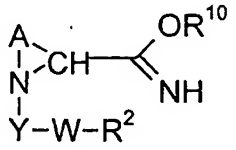
$$R^{1B}CSNHNH_2 \qquad (XVII)$$

wherein R^{1B} is as previously defined for this method, under conventional conditions.

7. The compounds of the formula (I) wherein R^1 is an optionally substituted 1,3,4-thiadiazolyl heteroaryl group and R^2, A, W and Y are as previously defined for a compound of the formula (I) can be prepared by reaction of a compound of the formula (XIV) wherein R^2, A, W, Y and R^{1A} are as previously defined for a compound of the formula (XIV) with a thionating agent, e.g. P_4S_{10} or Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-

dithia-2,4-diphosphetane-2,4-disulphide) in a suitable solvent, e.g. toluene, preferably at the reflux temperature thereof.

8. The compounds of the formula (I) wherein R^1 is an optionally substituted 1,2,4-triazol-3-yl heteroaryl group and R^2, A, W and Y are as previously defined for a compound of the formula (I) can be prepared by reaction of a compound of the formula:



(XVIII)

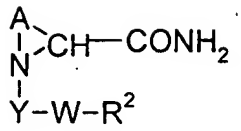
where R^2, A, W and Y are as previously defined for a compound of the formula (I) and R^{10} is C_1-C_4 alkyl, e.g. methyl or ethyl, with a compound of the formula:

$$R^{1A}NHNHCHO \qquad (XIX)$$

wherein R^{1A} is a relevant group corresponding to an optional substituent on the heteroaryl group as previously defined for R^1 for a compound of the formula (I).

The reaction may be carried out in a suitable solvent such as a mixture of toluene and 1,4-dioxane, and at the reflux temperature thereof.

A compound of the formula (XVIII) can be prepared by reaction of a compound of the formula:

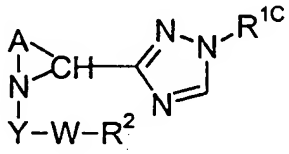


(XX)

wherein R^2, A, Y and W are as previously defined for a compound of the formula (I), with a tri(C_1-C_4 alkyl)oxonium hexafluorophosphate in dichloromethane.

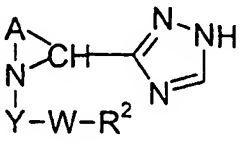
A compound of the formula (XX) can be prepared as described in Method (4) above or by treatment of a compound of the formula (XXIV) with ammonia.

9. The compounds of the formula:



(IA)

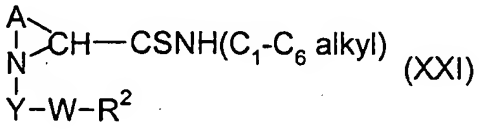
wherein R^2, A, W and Y are as previously defined for a compound of the formula (I) and R^{1C} is relevant group corresponding to a substituent on the heteroaryl group as previously defined for R^1 for a compound of the formula (I) that is linked to the ring nitrogen atom by a methylene group, can be prepared by alkylation of a compound of the formula:



(IB)

wherein R^2, A, W and Y are as previously defined for a compound of the formula (I) (a compound of the formula (IB) is prepared by the route described in Method (8) above, i.e. where R^{1A} is H) using an appropriate alkylating agent and under conventional conditions. Regioisomers may be formed in this reaction and they may be separated by chromatography.

10. The compounds of the formula (I) wherein R^1 is an optionally substituted 4-(C_1-C_6 alkyl)-4H-1,2,4-triazol-3-yl heteroaryl group and R^2, A, W and Y are as previously defined for a compound of the formula (I) can be prepared by reaction of a compound of the formula:



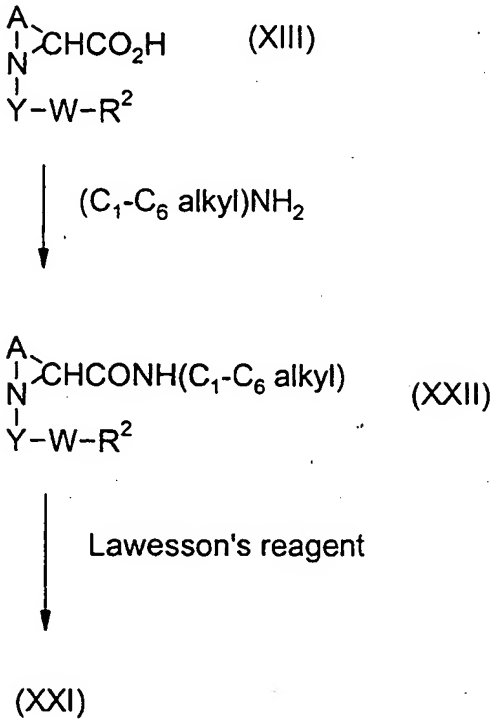
(XXI)

wherein R^2, A, W and Y are as previously defined for a compound of the formula (I), with a compound of the formula (XV) wherein R^{1A} is as previously defined for a compound of the formula (XV), in the presence of mercuric oxide.

The reaction may be carried out in a suitable solvent, e.g. 1,4-dioxane or dimethylacetamide, and at the reflux temperature.

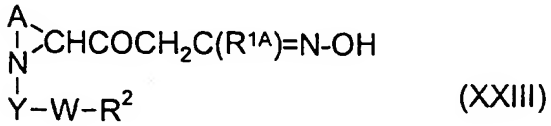
A compound of the formula (XXI) can be prepared under conventional conditions as shown in Scheme 2.

Scheme 2



wherein R^2, A, W and Y are as previously defined for a compound of the formula (I).

11. The compounds of the formula (I) wherein R^1 is an optionally 3-substituted isoxazol-5-yl heteroaryl group and R^2, A, W and Y are as previously defined for a compound of the formula (I) can be prepared by ring closure of a compound of the formula:

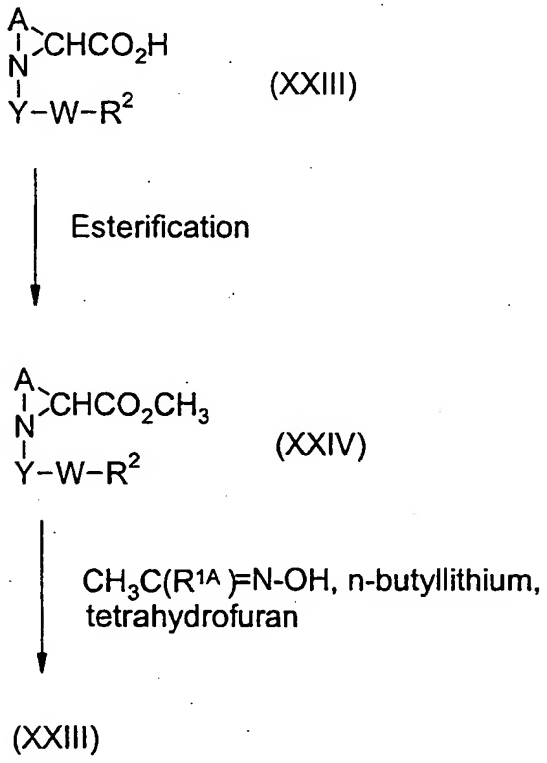


wherein R^2, A, W and Y are as previously defined for a compound of the formula (I) and R^{1A} is a relevant group corresponding to an optional substituent on the heteroaryl group as previously defined for R^1 for a compound of the formula (I).

The reaction may be carried out using mesyl chloride, triethylamine and dichloromethane as the solvent.

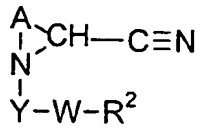
A compound of the formula (XXIII) can be prepared as shown in Scheme 3.

Scheme 3



wherein R^2, A, W, Y and R^{1A} are as previously defined for this method.

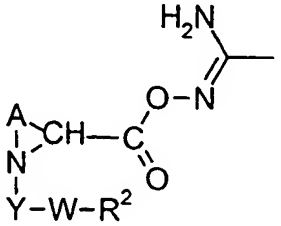
12. The compounds of the formula (I) wherein R^1 is an optionally substituted 1,2,3,4-tetraazol-5-yl heteroaryl group and R^2, A, W and Y are as previously defined for a compound of the formula (I) can be prepared by known methods such as, for example, by reaction of a compound of the formula (XXV):



(XXV)

where R^2, A, W and Y are as previously defined for a compound of the formula (I) with trimethylsilyl azide and dibutyltin oxide. The reaction may be carried out in a suitable solvent such as toluene and at the reflux temperature thereof. Compounds such as formula (XXV) can be N-alkylated using an appropriate alkylating agent and under conventional conditions regioisomers may be formed which can be separated be standard chromatogaphical methods.

13. The compounds of the formula (I) wherein R^1 is an optionally substituted 1,2,4-oxadiazol-5-yl heteroaryl group and R^2, A, W and Y are as previously defined for a compound of the formula (I) can be prepared by standard methods such as for example, by heat treatment of a compound of the formula (XXVI):



(XXV1)

where R^2, A, W and Y are as previously defined for a compound of the formula (I), in a suitable solvent such as xylene at reflux temperature. The compound of the formula (XXVI) can be prepared by reacting a compound of the formula (XIII) with a N^1-hydroxyimidamide, such as N^1-hydroxyethanimidamide. Suitable reaction conditions would be for example, in the presence of hydroxybenzotriazole hydrate, N-methyl morpholine, and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, in a solvent such as dichloromethane, at room temperature.

14. It will be appreciated that certain compounds of the formula (I) can be converted to other compounds of the formula (I) by conventional methods, e.g. using standard functional group interconversion techniques.

All of the above reactions and the preparations of novel starting materials using in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well-known to those skilled in the art with reference to literature precedents and the Examples and Preparations hereto.

A pharmaceutically acceptable salt of a compound of the formula (I) may be readily prepared by mixing together solutions of a compound of the formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

The affinity of the compounds of the formula (I) for FKBP-12 can be determined in vitro in a coupled colorimetric PPIase assay using similar procedures to published methods (e.g. see Kofron, J.L., et al., Biochemistry, 1991, 30, 6127-6134, Zarnt, T., et al., Biochem. J. 1995, 305, 159-164, Holt, D.A., et al., J. Am. Chem. Soc., 1993, 115, 9925-9938). In these methods, the cis-trans isomerisation of a hydrophobic amino acid-proline bond in a tetrapeptide substrate (e.g. the phenylalanine-proline bond in N-succinyl-ala-phe-pro-phe-p-nitroanilide [succinyl-AFPF-pNA]) can be determined by monitoring cleavage of pNA from the transPro-containing peptide by an excess of chymotrypsin.

The IC_{50} (the concentration of the compound of the formula (I) producing 50% inhibition) values were determined using the following assay methodology. Assay buffer (2.175ml) (50mM 4-(2-hydroxyethyl)-1-piperazineethanesulphonic acid (HEPES), 100mM NaCl, 1mM dithiothreitol (DTT), pH 8.0) is equilibrated to 10°C in a cuvette. 12.5µl of a solution of the present compound in DMSO, 250µl of a 60mg/ml solution of α-chymotrypsin in 1mM aqueous hydrochloric acid and then 50µl of a solution of human recombinant FKBP-12 (4.5µM) in assay buffer are added and mixed. The reaction is initiated by addition of 12.5µl of a solution of 20mM succinyl-AFPF-pNA in DMSO. The absorbance at 390nM is monitored for one minute collecting data every 0.25 second. Data are fitted with a first order rate equation with offset and the rate constant obtained corrected for the rate of uncatalysed isomerisation of the substrate. The rate constant determined at different inhibitor concentrations (10nM to 100µM) is expressed as % inhibition of the control rate constant. The IC_{50} is estimated using a non-linear least squares curve fitting routine of the sigmoidal dose response data.

$K_{i,app}$ (the apparent inhibition constant) was determined for the present compounds using the assay procedure described below. Assay buffer (2.175ml) (50mM HEPES, 100mM NaCl, 1mM DTT, pH 8.0) is equilibrated to 10°C in a cuvette. 12.5µl of a solution of the present compound in DMSO, 250µl of a 60mg/ml solution of α-chymotrypsin in 1mM aqueous hydrochloric acid and then 50µL of a solution of human recombinant FKBP-12 (1.5µM) in assay buffer are added and mixed. The reaction is initiated by adding 12.5µl of a solution of anhydrous succinyl-ALPF-pNA (100µM final concentration) in a 400mM solution of LiCl in trifluoroethanol. The absorbance at 390nM is monitored for 3 minutes collecting data every 0.5 second. Data are fitted with a first order rate equation with offset and the initial velocity (v) is calculated from the concentration of cis (re leu-pro bond)-succinyl-ALPF-pNA at t_o and the first order rate constant at different inhibitor concentrations (I). Data in the form $v_{inh}/v_{control}$ v. [I] are fitted with an equation for reversible tight binding inhibition to generate values for $K_{i,app}$ (see Morrison, J.F., et al, Comments Mol. Cell Biophys., 1985, 2, 347-368). This analysis is used when the $K_{i,app}$ approaches the concentration of FKBP-12 in the assay (30nM). Dixon analysis (see Dixon, M., Biochem. J.,1953, 55, 170-171) is used for generating values of $K_{i,app}$ for less potent compounds.

The same methodlogy is used to generate $K_{i,app}$ for FKBP52 with the following modifications: Forty microlitres human recombinant FKBP52 (5.2µM) is substituted for FKBP12 and 2.185ml assay buffer are used in the assay.

The compounds of the invention have inhibitory activity against the FKBP-12 enzyme. Early experimentation suggests that the compounds of the invention also have inhibitory activity against the FKPB-52 enzyme.

The neurite outgrowth promoting activity of the compounds of the formula (I) can be determined in explant cultures of embryonic chick dorsal root

ganglia. Dorsal root ganglia (DRG) are isolated aseptically according to the method of Bray (see "Culturing Nerve Cells", Ed. G.Banker and K. Goslin, MIT Press, Cambridge, MA, 1991, p.119). The individual ganglia were kept in Ca^{2+}/Mg^{2+}- free Tyrodes buffer on ice until a number of ganglia had been collected. Individual ganglia were then transferred into collagen-coated 24-well culture plates containing Neurobasal medium plus B27 supplements and incubated at 37°C in a 5% CO_2 atmosphere. The present compound was added after allowing 4 hours for the ganglia to attach. The explants were fixed and stained with Coomassie blue after 24 or 48 hours in culture. For each treatment 4 to 6 ganglia were analysed and scored by estimating the extent of neurite outgrowth relative to the diameter of the explant using image analysis. The present compounds were tested with and without 10ng/ml nerve growth factor (NGF) present and compared to outgrowth in the presence of 10ng/ml nerve growth factor alone.

An alternative system for measuring neurite outgrowth promoting activity of FKBP-12 PPIase inhibitors is the SH-SY-5Y neuroblastoma model described by Gold, B.G., et al, in Exp. Neurol. ,1997, 147(2), 269-278. Cells are maintained in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% Foetal calf serum (FCS), 50U/ml penicillin, 50µg/ml streptomycin at 37°C in a 7% CO_2 atmosphere. Cells are plated at $1x10^6$ cells per well and treated for 5 days with 400nM aphidicolin. Cells are then washed and treated with NGF at 10ng/ml ± various compound concentrations for 7 days to determine if the compounds promote neurite outgrowth in the presence of suboptimal NGF concentrations (and/or in the absence of NGF). Neurite outgrowth is determined by using image analysis to measure neurite lengths in 20 random fields.

The neurotrophic activity of the present compounds can be evaluated in vivo using the sciatic nerve crush model in rat as a model for peripheral nerve regeneration (see Bridge, P.M., et al. , Experimental Neurology, 1994, 127,

284-290, Medinaceli, L., et al., Expl. Neurology, 1982, 77, 634-643, Gold, B.G.,et al., Restorative Neurology and Neuroscience, 1994, 6, 287-296), the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine models in various species as a model for regeneration in Parkinson's disease (see Mokry, J., Physiol. Res., 1995, 44(3), 143-150) and fimbria-fornix lesions as a model for regeneration in Alzheimer's disease (see Cassel, J.C., Duconseille, E., Jeltsch, H. and Will, B., Prog. Neurol., 1997, 51, 663-716).

The compounds of the formula (I) can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, the compounds of the formula (I) can be administered orally or sublingually in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate or controlled release applications.

Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc may be included.

Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose or milk sugar as well as high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compounds of the formula (I) may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

The compounds of the formula (I) can also be injected parenterally, for example, intravenously, intraperitoneally, intrathecally, intraventricularly, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion techniques. They are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of the formula (I) will usually be from 1 microgram/kg to 25 mg/kg (in single or divided doses).

Thus tablets or capsules of the compound of the formula (I) may contain from 0.05 mg to 1.0 g of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention.

The compounds of formula (I) can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container or a nebuliser with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark] or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable

gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the formula (I) and a suitable powder base such as lactose or starch.

Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 20μg to 20 mg of a compound of the formula (I) for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 20μg to 20 mg which may be administered in a single dose or, more usually, in divided doses throughout the day.

Alternatively, the compounds of the formula (I) can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. The compounds of the formula (I) may also be transdermally administered by the use of a skin patch. They may also be administered by the ocular route, particularly for treating neurological disorders of the eye.

For ophthalmic use, the compounds can be formulated as micronised suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

For application topically to the skin, the compounds of the formula (I) can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the

following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The compounds of the formula (I) can also be administered together with other neutrophic agents such as neurotrophic growth factor (NGF), glial derived growth factor, brain derived growth factor, ciliary neurotrophic factor and/or neurotrophin-3. The dosage level of the neurotrophic agent will depend upon the neurotrophic effectiveness of the combination and the route of administration used.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

Thus the invention further provides:-

(i) a pharmaceutical composition comprising a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient, diluent or carrier;

(ii) a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a medicament;

(iii) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of neuronal degeneration;

(iv) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the promotion of neuronal regeneration and outgrowth;

(v) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of a neurological disease or disorder such as a neurodegenerative disease;

(vi) use as in (v) where the neurological disease or disorder is selected from the group consisting of senile dementia (Alzheimer's disease) and other dementias, amyotrophic lateral sclerosis and other forms of motor neuron disease, Parkinson's disease, Huntington's disease, neurological deficits associated with stroke, all forms of degenerative disease affecting the central or peripheral nervous system (e.g. cerebellar-brainstem atrophies, syndromes of progressive ataxias), all forms of muscular dystrophy, progressive muscular atrophies, progressive bulbar muscular atrophy, physical or traumatic damage to the central or peripheral nervous system (e.g. spinal cord), herniated, ruptured or prolapsed intervertebrae disc syndromes, cervical spondylosis, plexus disorders, thoracic outlet syndromes, all forms of peripheral neuropathy (both diabetic and non-diabetic), trigeminal neuralgia, glossopharyngeal neuralgia, Bell's Palsy, all forms of auto-immune related disease resulting in damage of the central or peripheral nervous system (e.g. multiple sclerosis, myasthenia gravis, Guillain-Barré syndrome), AIDS related disorders of the nervous system, dapsone ticks, bulbar and retrobulbar affections of the optic nerve (e.g. retinopathies and retrobulbar neuritis), hearing disorders such as tinnitus, and prion diseases;

(vii) use as (vi) where the neurological disease or disorder is senile dementia (Alzheimer's disease) or another dementia, amyotrophic lateral sclerosis or another form of motor neuron disease, Parkinson's disease, Huntington's disease, a neurological deficit associated with stroke, physical or traumatic damage to the central or peripheral nervous system

(e.g. spinal cord), a peripheral neuropathy (either diabetic or non-diabetic), multiple sclerosis or a hearing disorder such as tinnitus;

(viii) a method of treatment of a human to treat neuronal degeneration which comprises treating said human with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(ix) a method of treatment of a human to promote neuronal regeneration and outgrowth which comprises treating said human with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(x) a method of treatment of a human to treat a neurological disease or disorder such as a neurodegenerative disease which comprises treating said human with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(xi) a method as in (x) where the neurological disease or disorder is selected from the group consisting of senile dementia (Alzheimer's disease) and other dementias, amyotrophic lateral sclerosis and other forms of motor neuron disease, Parkinson's disease, Huntington's disease, neurological deficits associated with stroke, all forms of degenerative disease affecting the central or peripheral nervous system (e.g. cerebellar-brainstem atrophies, syndromes of progressive ataxias), all forms of muscular dystrophy, progressive muscular atrophies, progressive bulbar muscular atrophy, physical or traumatic damage to the central or peripheral nervous system (e.g. spinal cord), herniated, ruptured or prolapsed intervertebrae disc syndromes, cervical spondylosis, plexus disorders, thoracic outlet syndromes, all forms of peripheral neuropathy (both diabetic and non-diabetic), trigeminal neuralgia, glossopharyngeal neuralgia, Bell's Palsy, all forms of auto-immune related disease resulting in damage of the central or peripheral nervous system (e.g.

multiple sclerosis, myasthenia gravis, Guillain-Barré syndrome), AIDS related disorders of the nervous system, dapsone ticks, bulbar and retrobulbar affections of the optic nerve (e.g. retinopathies and retrobulbar neuritis), hearing disorders such as tinnitus, and prion diseases;

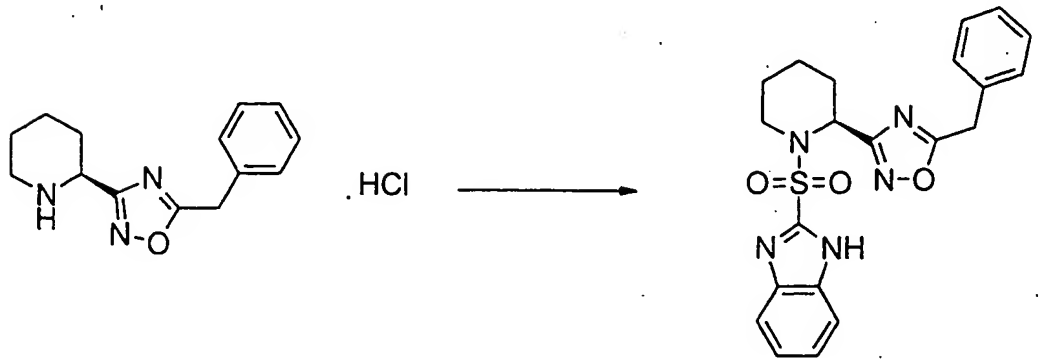
(xii) a method as in (xi) where the neurological disease or disorder is senile dementia (Alzheimer's disease) or another dementia, amyotrophic lateral sclerosis or another form of motor neuron disease, Parkinson's disease, Huntington's disease, a neurological deficit associated with stroke, physical or traumatic damage to the central or peripheral nervous system (e.g. spinal cord), a peripheral neuropathy (either diabetic or non-diabetic), multiple sclerosis or a hearing disorder such as tinnitus; and

(xiii) any novel intermediates described herein.

The following Examples illustrate the preparation of the compounds of the formula (I). The ACD/IUPAC Pro software programme was used as the basis for naming the prepared compounds.

Example 1

1*H*-Benzo[*d*]imidazol-2-yl [(2*S*)-2-(5-benzyl-1,2,4-oxadiazol-3-yl)-1-piperidyl]sulfone



Ethyldiisopropylamine (383µl) was added to a mixture of 5-benzyl-3-[(2*S*)-2-piperidyl]-1,2,4-oxadiazole hydrochloride (279.8mg) [see Preparation 7] and 1*H*-benzo[*d*]imidazole-2-sulfonyl chloride (325mg) [see Preparation 8] in dichloromethane (5ml). The reaction mixture was stirred at room temperature for 18 hours after which time the mixture was diluted with dichloromethane and washed with aqueous sodium hydrogen carbonate solution. The organic layer was separated, dried over magnesium sulphate, and the solvent removed under reduced pressure. The residue was chromatographed on silica gel eluting with a solvent gradient of 0:100 changing to 20:80, by volume, ethyl acetate:hexane to give the product as a white solid. This solid was dissolved in dichloromethane and the solvent was removed under reduced pressue to give 1*H*-benzo[*d*]imidazol-2-yl [(2*S*)-2-(5-benzyl-1,2,4-oxadiazol-3-yl)-1-piperidyl] sulfone (245mg) as a white solid.

^{1}H-NMR ($CDCl_3$) δ: 10.80 (1H, s), 7.80 (1H, s), 7.40-7.10 (8H, m), 5.50 (1H, m), 3.95 (1H, d), 3.85 (2H, q), 3.20 (1H, m), 2.25 (1H, d), 2.05 (1H, m), 1.80-1.50 (4H, m) ppm.

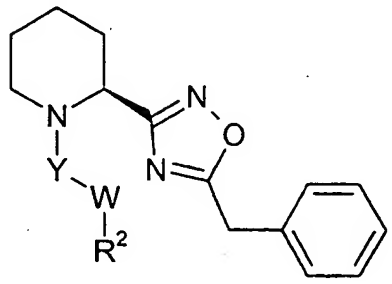
MS (mass spectrometry): 424 (MH^+).

Analysis: Found C,58.07; H, 4.97; N, 15.81; $C_{21}H_{21}N_5O_3S$. 0.6 H_2O requires C, 58.08; H, 5.15; N, 16.13%.

Rotation: $[\alpha]_D^{25}$ = -56.37° (c = 0.1, methanol).

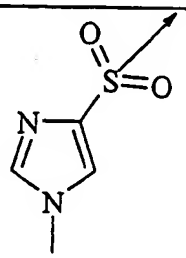
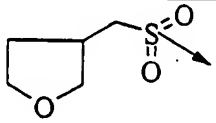
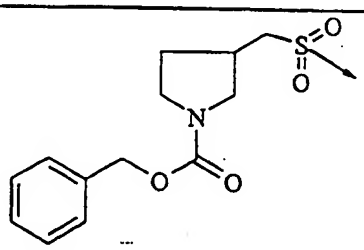
Examples 2 - 8

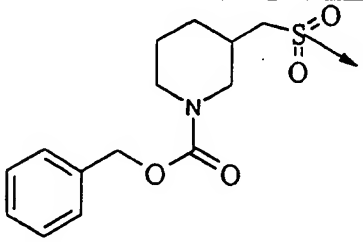
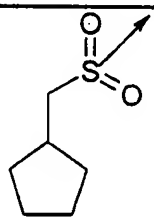
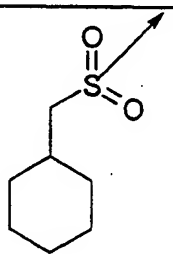
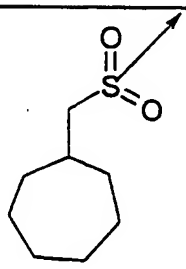
The compounds of the following tabulated Examples (Table 1) of the general formula :



were prepared by a similar method to that of Example 1 using the appropriate sulphonyl chloride and 5-benzyl-3-[(2*S*)-2-piperidyl]-1,2,4-oxadiazole hydrochloride [see Preparation 7].

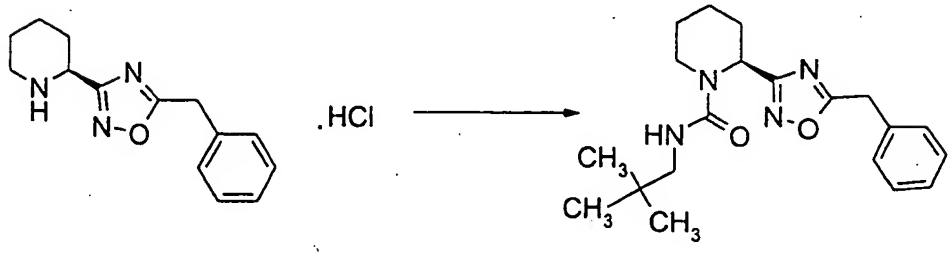
Table 1

Example no.	Starting material prep.no.	Y-W-R^2	Analytical data
2			^{1}H-NMR ($CDCl_3$) δ : 7.40-7.2-(6H, m), 7.15 (1H, s), 5.40 (1H, m), 4.20 (2H, s), 3.90 (1H, d), 3.60 (3H, s), 3.45 (1H, m), 2.00 (2H, m), 1.60 (4H, m). Analysis : Found C, 55.61; H, 5.50; N, 17.87, $C_{18}H_{21}N_5O_3S$ requires C, 55.80; H, 5.46; N, 18.07%.
3	11		^{1}H-NMR ($CDCl_3$) δ : 7.40-7.20 (5H, m), 5.25 (1H, s), 4.20 (2H, s), 3.95 (1H, m), 3.80-3.60 (3H, m), 3.45 (1H, m), 3.20-3.00 (3H, m), 2.70 (1H, m), 2.25 (1H, m), 2.10 (1H, m), 1.95 (1H, m), 1.80-1.40 (5H, m). Analysis : Found C, 56.98; H, 6.39; N, 10.21; $C_{19}H_{25}N_3O_4S$ 0.1 CH_2Cl_2 requires C, 57.17; H, 6.33; N, 10.46%.
4	58		^{1}H-NMR ($CDCl_3$) δ : 7.40-7.20 (10H, m), 5.30 (1H, m), 5.15 (2H, s), 4.20 (2H, s), 3.80 (2H, m), 3.55 (1H, m), 3.35 (1H, m), 3.20-3.00 (4H, m), 2.70 (1H, m), 2.40 (1H, d), 2.00 (1H, m), 1.80-1.50 (6H, m). Analysis : Found C, 61.52; H, 6.11; N, 10.61; $C_{27}H_{32}N_4O_5S$ requires C, 61.81; H, 6.15; N, 10.68%.

5	62		^{1}H-NMR (d6-DMSO) δ : 7.40-7.20 (10H, m), 5.15 (1H, m), 5.00 (2H, s), 4.30 (2H, s), 4.15 (1H, d), 4.05 (1H, m), 3.80 (1H, m), 3.60 (1H, m), 3.00 (3H, m), 2.80 (1H, m), 2.60 (1H, m), 2.05 (1H, d), 1.80 (3H, m), 1.55 (3H, m), 1.40-1.10 (3H, m). Analysis : Found C, 62.11; H, 6.34; N, 10.27; $C_{28}H_{34}N_4O_5S$ requires C, 62.43; H, 6.36; N, 10.40%.
6	65		MS : 390 (MH^+). Analysis : Found C, 61.40; H, 6.96; N, 10.76; $C_{20}H_{27}N_3O_3S$ requires C, 61.67; H, 6.99; N, 10.79%. $[\alpha]_D$ = -41.93° (C = 0.1, methanol).
7			^{1}H-NMR ($CDCl_3$) δ : 7.40-7.20 (5H, m), 5.35 (1H, m), 4.25 (2H, s), 3.80 (1H, d), 3.20 (1H, m), 2.90 (2H, m), 2.25 (1H, d), 2.00 (3H, m), 1.80-1.40 (8H, m), 1.30-1.10 (3H, m), 1.00 (2H, m). Analysis : Found C, 62.47; H, 7.29; N, 10.33; $C_{21}H_{29}N_3O_3S$ requires C, 62.50; H, 7.24; N, 10.41%
8	68		^{1}H-NMR ($CDCl_3$) δ : 7.40-7.20 (5H, m), 5.25 (1H, d), 4.20 (2H, m), 3.75 (1H, d), 3.20 (1H, t), 2.90 (2H, m), 2.25 (1H, d), 2.10 (1H, m), 2.00-1.80 (3H, m), 1.70-1.40 (12H, m), 1.25 (2H, m). Analysis : Found C, 62.97; H, 7.42; N, 9.99; $C_{22}H_{31}N_3O_3S$ requires C, 63.28; H, 7.48; N, 10.06%

Example 9

*N*1-Neopentyl-((2*S*)-2-(5-benzyl-1,2,4-oxadiazol-3-yl))-1-piperidinecarboxamide



Triphosgene (45mg) in dichloromethane (2ml) was added dropwise to a solution of 5-benzyl-3-[(2*S*)-2-piperidyl]-1,2,4-oxadiazole hydrochloride (140mg) [see Preparation 7] and triethylamine (139ml) in dichloromethane (2ml). The reaction mixture was stirred at room temperature for 1hour. A solution of neopentylamine (78mg) and triethylamine (70μl) in dichloromethane was added to the mixture and stirred for 18 hours. The reaction mixture was then diluted with dichloromethane and water, the organic phase was separated, dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 90:10 changing to 83:17, by volume, hexane : ethyl acetate to afford *N*1-neopentyl-((2*S*)-2-(5-benzyl-1,2,4-oxadiazol-3-yl))-1-piperidinecarboxamide (66mg) as a clear oil.

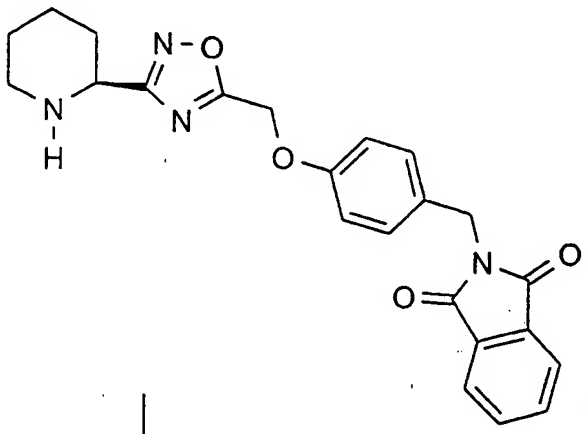
^{1}H-NMR ($CDCl_3$) δ : 7.30 (5H, m), 5.50 (1H, s), 4.80 (1H, s), 4.20 (2H, s), 3.70 (1H, d), 3.20-3.00 (3H, m), 2.25 (1H, d), 1.90 (1H, m), 1.70-1.40 (4H, m), 0.90 (9H, s).

Rotation : $[\alpha]_D^{25}$ = -43.41° (c = 0.1, methanol).

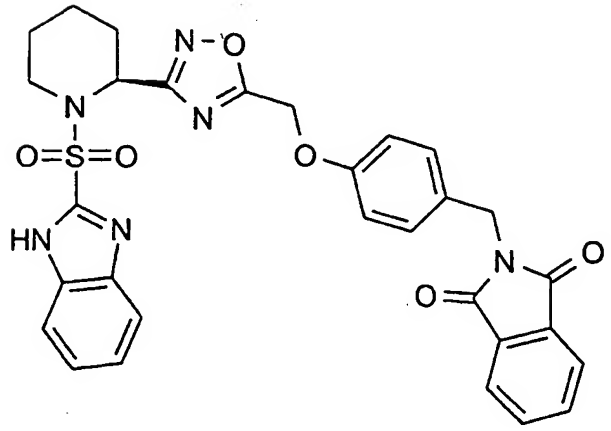
Analysis : Found C, 66.95; H, 7.99; N, 15.18; $C_{20}H_{28}N_4O_2.0.2\ H_2O$ requires C, 66.71; H, 7.95; N, 15.56%.

Example 10

2-[4-(3-[(2*S*)-1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzyl]-1,3-isoindolinedione



.HCl



The title compound was prepared by a similar method to Example 1 from 2-[4-(3-[(2*S*)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzyl]-1,3-isoindolinedione hydrochloride [see Preparation 15] and 1*H*-benzo[*d*]imidazole-2-sulfonyl chloride [see Preparation 8] to afford 2-[4-(3-[(2*S*)-1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzyl]-1,3-isoindolinedione (956mg).

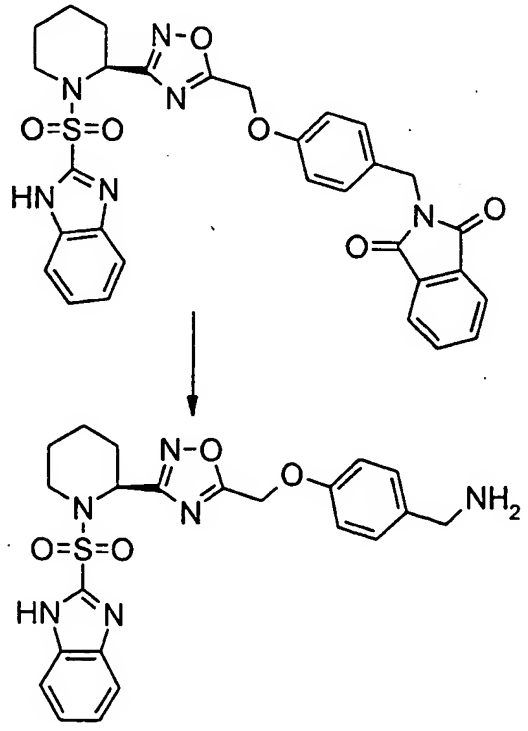
^{1}H-NMR ($CDCl_3$) δ : 7.85 (2H, m), 7.75 (2H, m), 7.70 (2H, bs), 7.40 (2H, d), 7.30 (2H, d), 6.80 (2H, d), 5.60 (1H, d), 4.80 (4H, 2xd), 4.00 (1H, d), 3.20 (1H, t), 2.30 (1H, d), 2.10 (1H, m), 1.80-1.40 (4H, m).

Analysis : Found C, 59.04; H, 4.60; N, 13.24; $C_{30}H_{26}N_6O_6S.0.3EtOAc.0.5\ H_2O$ requires C, 59.10; H, 4.67; N, 13.25% (EtOAc = ethyl acetate).

$[\alpha]_D^{25}$ = -46° (c = 0.1, methanol).

Example 11

4-(3-[(2*S*)-1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzylamine



2-[4-(3-[(2*S*)-1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzyl]-1,3-isoindolinedione (885mg) [see Example 10] was added to a solution of 33% w/w methylamine in ethanol (2.2ml). The reaction mixture was stirred at room temperature for 5 hours after which time the solvent was removed under reduced pressure. The resulting solid was dissolved in 1N aqueous hydrochloric acid solution and dichloromethane. The aqueous layer was then separated and basified to pH 12 with 0.88 aqueous ammonia solution. The mixture was then extracted with ethyl acetate, the organic layer dried over magnesium sulphate and the solvent removed under reduced pressure to afford 4-(3-[(2*S*)-1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzylamine (369mg) as a white solid.

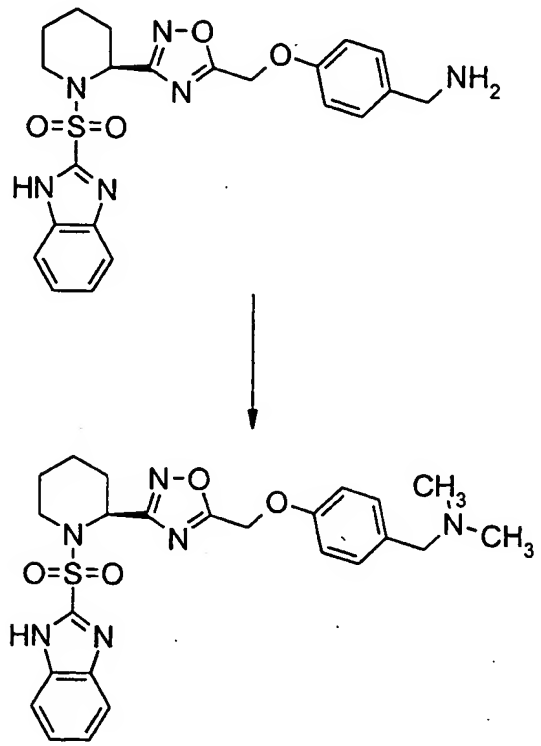
^{1}H-NMR (d_6- DMSO) δ : 7.60 (2H, d), 7.35 (2H, d), 7.20 (2H, d), 7.00 (2H, d), 5.40 (1H, s), 5.20 (2H, q), 3.90 (1H, d), 3.80 (2H, s), 3.20 (3H, bs), 1.90 (1H, d), 1.80 (1H, m), 1.50 (2H, t), 1.30 (2H, m).

Analysis : Found C, 55.91; H, 5.10; N, 17.68; $C_{22}H_{24}N_6O_4S$. 0.1 H_2O requires C, 56.18; H, 5.19; N, 17.87%.

$[\alpha]_D^{25}$ = -54° (c = 0.1, methanol).

Example 12

N-[4-(3-[(2*S*)-1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzyl]-*N*,*N*-dimethylamine



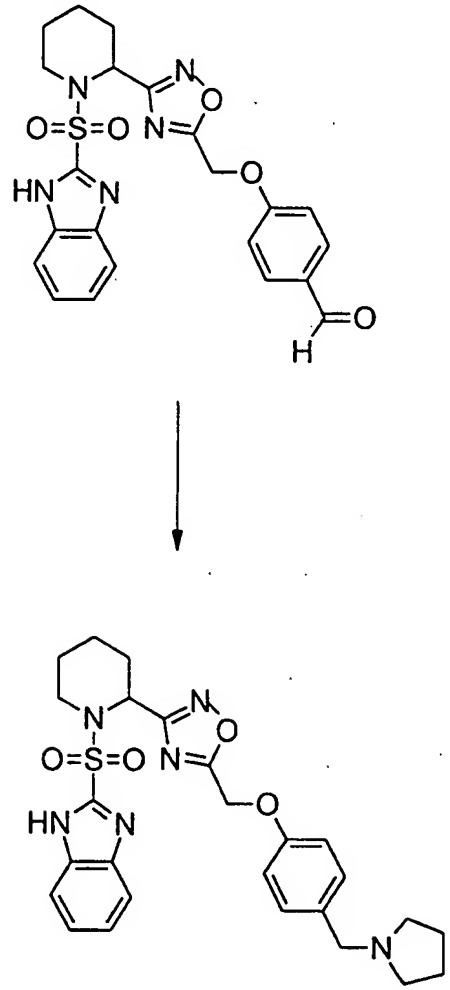
Formaldehyde (37% w/w aqueous solution) (65μl) was added to a solution of 4-(3-[(2*S*)-1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzylamine (75mg) [see Example 11] in acetonitrile (2ml), followed by sodium triacetoxyborohydride (170mg). The reaction mixture was stirred at room temperature for 18 hours, after which time glacial acetic acid was added until the solution was at pH 7.0. The mixture was then diluted with dichloromethane and washed with saturated aqueous sodium hydrogen carbonate solution. The organic layer was separated, dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with a solvent

^{1}H-NMR ($CDCl_3$) δ : 7.70 (2H, m), 7.40 (2H, d), 7.25 (2H, d), 6.80 (2H, d), 5.60 (1H, d), 4.90 (2H, q), 4.00 (1H, d), 3.40 (2H, s), 3.20 (1H, m), 2.40 (1H, d), 2.20 (6H, s), 2.16 (1H, m), 1.80 (1H, m), 1.30 (1H, m), 0.90 (2H, m).

Rotation : $[\alpha]_D^{25}$ = - 48.41° (c = 0.1, methanol).
Analysis : Found C, 58.15; H, 6.01; N, 16.02; $C_{24}H_{28}N_6O_4S$. 0.2 hexane. 0.5 H_2O requires C, 58.07; H, 5.84; N,16.12%.

Exampl 13

3-[1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-5-[4-(1-pyrrolidylmethyl)phenoxy]methyl-1,2,4-oxadiazole



Pyrrolidine (19µl) was added to a solution of 4-(3-[1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzaldehyde (85mg) [see Preparation 22] in tetrahydrofuran (10ml). Sodium triacetoxyborohydride (64mg) was added followed by glacial acetic acid (11.5µl). The reaction mixture was stirred under an atmosphere of nitrogen for 6 hours. Sodium triacetoxyborohydride (21mg) was added and the mixture was stirred for 56 hours after which time the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with

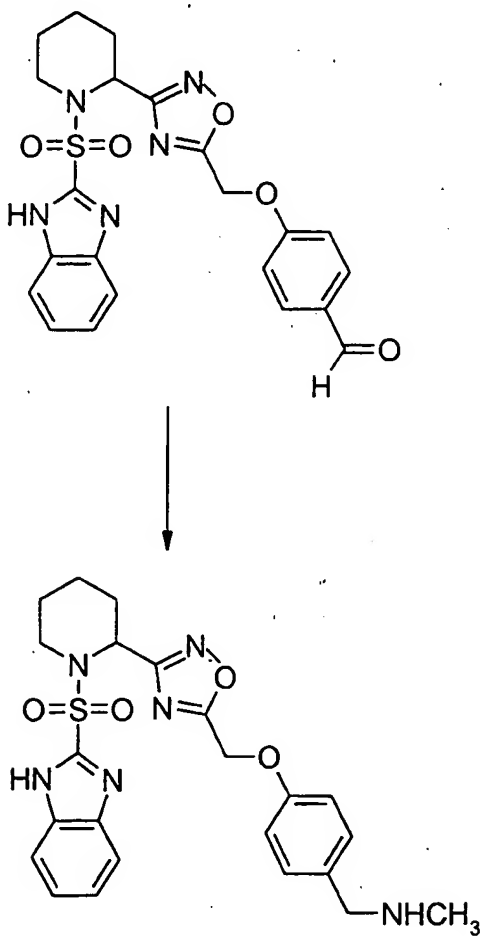
a solvent gradient of 97.5:2.5:0.25 changing to 95:5:0.5, by volume, dichloromethane : methanol : 0.88 aqueous ammonia solution to afford 3-[1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-5-[4-(1-pyrrolidylmethyl)phenoxy]methyl-1,2,4-oxadiazole (90mg) as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 7.70 (2H, s), 7.40 (2H, m), 7.30 (2H, m), 6.80 (2H, m), 5.60 (1H, d), 4.90 (2H, q), 4.00 (1H, d), 3.60 (2H, s), 3.20 (1H, m), 2.60 (4H, bs), 2.30 (1H, d), 2.00-0.95 (8H, m).

Analysis : Found C, 59.24; H, 5.94; N, 15.10; $C_{26}H_{30}N_6O_4S$. H_2O. 0.3 hexane requires C, 59.20; H, 6.04; N, 14.90%.

Example 14

_N_-[4-(3-[1-(1_H_-Benzo[_d_]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzyl]-_N_-methylamine



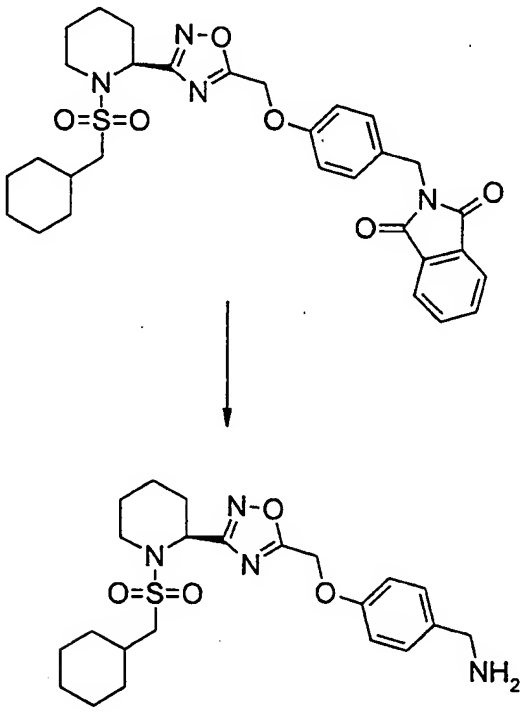
The title compound was prepared by a similar method to Example 13 from 4-(3-[1-(1_H_-benzo[_d_]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzaldehyde [see Preparation 22] and methylamine hydrochloride to afford _N_-[4-(3-[1-(1_H_-benzo[_d_]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzyl]-_N_-methylamine as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 7.70 (2H, bs), 7.40 (2H, m), 7.30 (2H, m), 6.80 (2H, m), 5.60 (1H, d), 4.90 (2H, q), 4.00 (1H, d), 3.75 (2H, s), 3.20 (1H, m), 2.50 (3H, s), 2.40-2.00 (4H, m), 1.80 (2H, m).

Analysis : Found C, 54.74; H, 5.50; N, 15.56; $C_{23}H_{26}N_6O_4S$. H_2O. 0.2 CH_2Cl_2. 0.2 hexane requires C, 54.97; H, 5.60; N, 15.76%.

Example 15

4-[3-((2S)-1-[Cyclohexylmethylsulfonyl]-2-piperidyl)-1,2,4-oxadiazol-5-ylmethoxy]benzylamine



The title compound was prepared by a similar method to Example 11 from 2-[4-(3-[(2S)-1-cyclohexylmethylsulfonyl-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzyl]-1,3-isoindolinedione [see Preparation 23] and methylamine. The crude product was purified by column chromatography on silica gel eluting

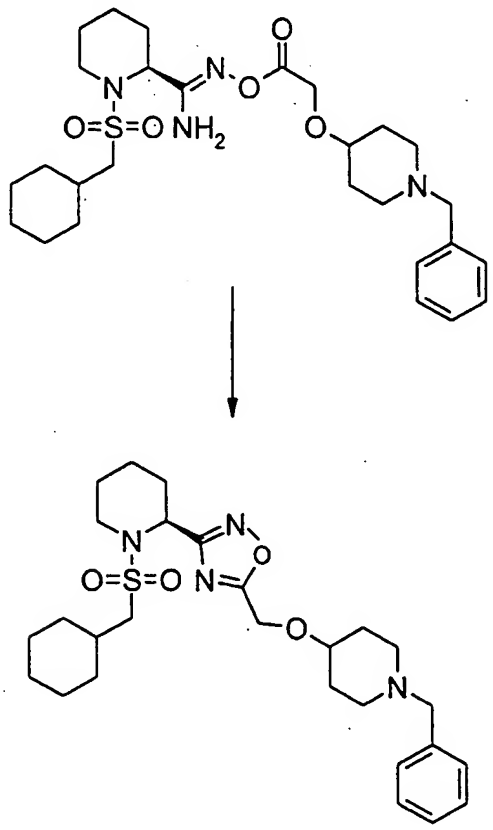
with a solvent gradient of 100:0:0 changing to 90:10:1, by volume, dichloromethane : methanol : 0.88 aqueous ammonia solution to afford 4-[3-((2S)-1-[cyclohexylmethylsulfonyl]-2-piperidyl)-1,2,4-oxadiazol-5-ylmethoxy]benzylamine as a colourless oil.

^{1}H-NMR ($CDCl_3$) δ : 7.30 (2H, d), 7.00 (2H, d), 5.40 (1H, d), 5.30 (2H, s), 3.85 (2H, s), 3.80 (1H, d), 3.20 (1H, m), 2.90 (2H, m), 2.30 (1H, d), 2.00-1.00 (18H, m).

Accurate MS : 449.2216 (MH^+).

Example 16

5-[(1-Benzyl-4-piperidyl)oxymethyl]-3-[(2*S*)-1-cyclohexylmethylsulfonyl-2-piperidyl]-1,2,4-oxadiazole



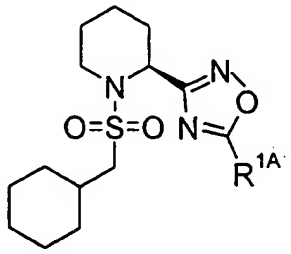
The compound of Preparation 29 (464mg) was dissolved in pyridine (5 ml) and heated under reflux for 18 hours. The reaction mixture was then cooled and the solvent removed under reduced pressure. The residue was partitioned between ethyl acetate and water, the organic layer was separated , dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 99:0.4:0.2 changing to 93:7:1, by volume, dichloromethane : methanol : 0.88 aqueous ammonia solution to afford 5-[(1-benzyl-4-piperidyl)oxymethyl]-3-[(2*S*)-1-cyclohexylmethylsulfonyl-2-piperidyl]-1,2,4-oxadiazole (357mg) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ : 7.30 (5H, m), 5.30 (1H, d), 4.80 (2H, s), 3.80 (1H, d), 3.55 (1H, m), 3.50 (2H, s), 3.20 (1H, m), 2.90 (2H, m), 2.75 (2H, m), 2.20 (3H, m), 2.00 (6H, m), 1.70 (8H, m), 1.50-1.00 (6H, m).

Analysis : Found C, 62.53; H, 7.84; N, 10.82; $C_{27}H_{40}N_4O_4S$ requires C, 62.76; H, 7.80; N, 10.84%.

Examples 17 - 22

The compounds of the following tabulated Examples (Table 2) of the general formula:



were prepared by a similar method to Example 16 from the corresponding hydroxyamidine derivatives and pyridine.

Table 2

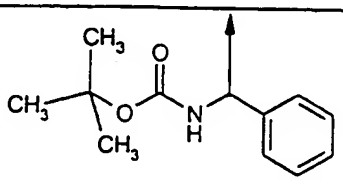
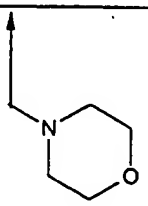
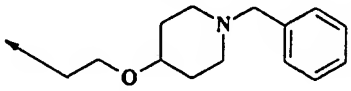
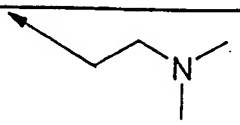
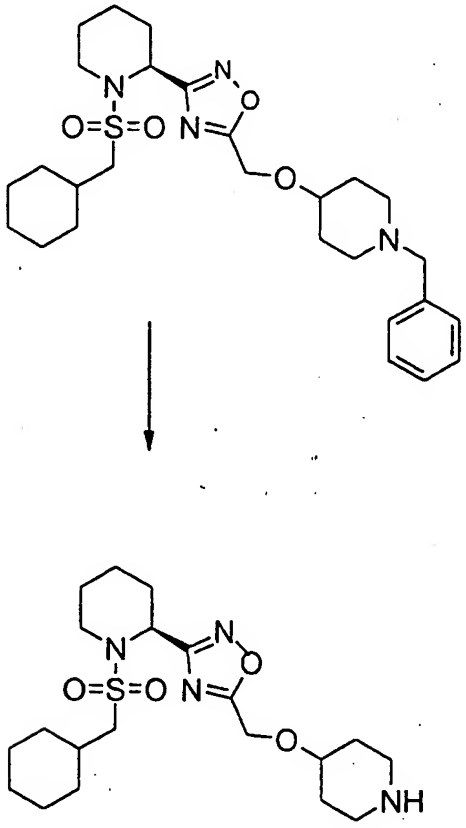
Example no.	Starting material prep.no.	R^{1A}	Analytical data
17	31		^{1}H-NMR ($CDCl_3$) δ : 7.40 (5H, m), 6.10 (1H, bs), 5.50 (1H, s), 5.35 (1H, s), 3.80 (1H, d), 3.20 (1H, q), 2.90 (2H, m), 2.25 (1H, d), 2.00 (4H, m), 1.80-1.00 (21H, m). Analysis : Found C, 58.53; H, 7.33; N, 10.18; $C_{26}H_{38}N_4O_5S$. 0.8 H_2O requires C, 58.58; H, 7.48; N, 10.51%.
18	32		^{1}H-NMR ($CDCl_3$) δ : 5.35 (1H, d), 3.80 (2H, m), 3.75 (4H, m), 3.25 (1H, t), 2.90 (2H, m), 2.60 (4H, t), 2.25 (1H, d), 2.00 (4H, m), 1.70 (6H, m), 1.40-1.00 (7H, m). Analysis : Found C, 54.67; H, 7.82; N, 13.23; $C_{19}H_{32}N_4O_4S$. 0.1 CH_2Cl_2 requires C, 54.49; H, 7.71; N, 13.31%.
19	36		^{1}H-NMR ($CDCl_3$) δ : 7.30 (5H, m), 5.30 (1H, s), 3.90 (2H, m), 3.80 (1H, d), 3.45 (2H, s), 3.40 (1H, m), 3.20 (1H, m), 3.15 (2H, m), 2.95 (2H, m), 2.70 (2H, m), 2.25 (1H, d), 2.10 (2H, t), 2.00-1.00 (20H, m). Analysis : Found C, 61.49; H, 7.82; N, 10.07; $C_{28}H_{42}N_4O_4S$. 0.75 H_2O requires C, 61.79; H, 8.06; N, 10.29%.

Table 2 (continued)

20	69		^{1}H-NMR ($CDCl_3$) δ : 5.30 (1H, d), 3.80 (1H, d), 3.20 (1H, t), 3.05 (2H, t), 2.90 (2H, m), 2.80 (2H, t), 2.25 (6H, s), 2.20 (1H, s), 2.00-1.85 (4H, m), 1.70 (6H, m), 1.50 (1H, m), 1.30-1.00 (5H, m). Analysis : Found C, 56.13; H, 8.44; N, 14.44; $C_{18}H_{32}N_4O_3S$ requires C, 56.22; H, 8.39; N, 14.57%. Rotation : $[\alpha]_D$ = -25.81°(c = 0.1, methanol).
21	70	H	^{1}H-NMR ($CDCl_3$) δ : 8.70 (1H, s), 5.40 (1H, d), 3.80 (1H, d), 3.25 (1H, t), 2.95 (2H, m), 2.30 (1H, d), 2.00 (4H, m), 1.80-1.60 (6H, m), 1.50 (1H, m), 1.35-1.05 (5H, m). Analysis : Found C, 53.61; H, 7.43; N, 13.09; $C_{14}H_{23}N_3O_3S$ requires C, 53.65; H, 7.40; N, 13.41%. Rotation : $[\alpha]_D$ = -27.60° (c = 0.1, methanol).
22	71	CH_3	^{1}H-NMR ($CDCl_3$) δ : 5.30 (1H, d), 3.80 (1H, d), 3.25 (1H, t), 2.95 (2H, m), 2.60 (3H, s), 2.25 (1H, d), 2.00 (4H, m), 1.80-1.60 (6H, m), 1.50 (1H, m), 1.40-1.05 (5H, m). Analysis : Found C, 55.19; H, 7.80; N, 12.40; $C_{15}H_{25}N_3O_3S$. 0.1EtOAc requires C, 55.01; H, 7.73; N, 12.50%. Rotation : $[\alpha]_D$ = -26.70° (c = 0.1, methanol).

Example 23

3-[(2*S*)-1-Cyclohexylmethylsulfonyl-2-piperidyl]-5-[4-piperidyloxymethyl]-1,2,4-oxadiazole



α-Chloroethyl chloroformate (95μl) was added to a solution of 5-[(1-benzyl-4-piperidyl)oxymethyl]-3-[(2*S*)-1-cyclohexylmethylsulfonyl-2-piperidyl]-1,2,4-oxadiazole (325mg) [see Example 16] in dichloromethane (20ml) at 0°C . The reaction mixture was stirred for 1.5 hours after which time the dichloromethane was removed under reduced pressure and the residue dissolved in methanol. The mixture was then heated under reflux for 2 hours, the solvent removed under reduced pressure and the residue partitioned between diethyl ether and 2N aqueous hydrochloric acid solution. The aqueous layer was washed twice

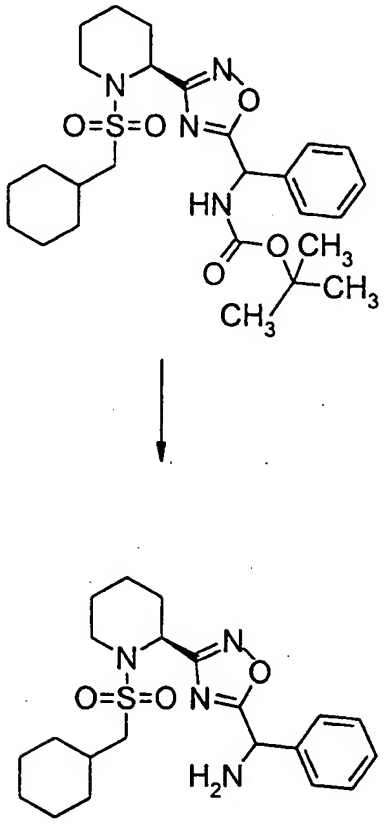
with diethyl ether and then neutralised (pH7) with sodium hydrogen carbonate. The aqueous layer was extracted with ethyl acetate, dried over magnesium sulphate and the solvent removed under reduced pressure to afford 3-[(2*S*)-1-cyclohexylmethylsulfonyl-2-piperidyl]-5-[4-piperidyloxymethyl]-1,2,4-oxadiazole (170mg) as a brown oil.

^{1}H-NMR ($CDCl_3$) δ : 5.30 (1H, d), 4.80 (2H, s), 3.80 (1H, d), 3.60 (1H, m), 3.25 (1H, m), 3.15 (2H, m), 2.90 (2H, m), 2.75 (2H, m), 2.30 (1H, d), 2.00 (6H, m), 1.80-1.00 (15H, m).

Analysis : Found C, 54.69; H, 8.06; N, 12.71; $C_{20}H_{34}N_4O_4S.0.2\ CH_2Cl_2$ requires C, 54.70; H, 7.82; N, 12.63%.

Exampl 24

(3-[(2*S*)-1-Cyclohexylmethylsulfonyl-2-piperidyl]-1,2,4-oxadiazol-5-yl)(phenyl)methylamine



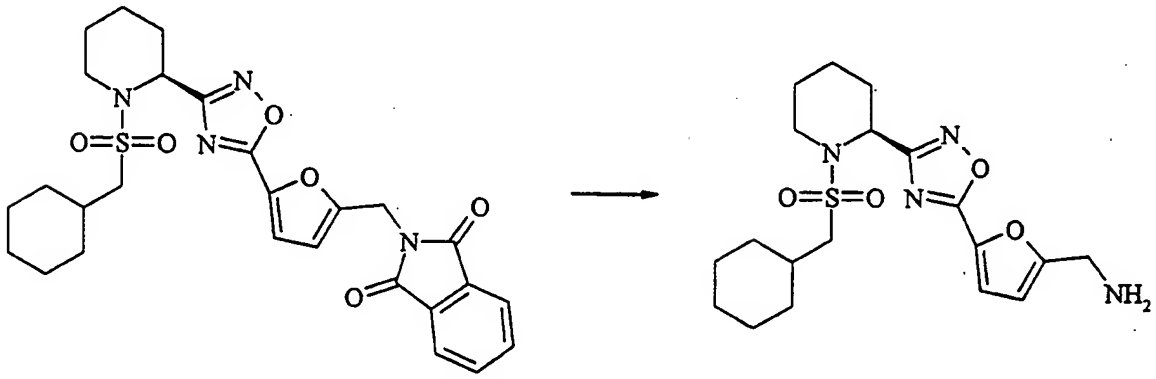
The title compound was prepared by the method of Preparation 7 from *tert*-butyl *N*-[(3-[(2*S*)-1-cyclohexylmethylsulfonyl-2-piperidyl]-1,2,4-oxadiazol-5-yl)(phenyl)methyl]carbamate [see Example 17]. The crude product was purified by high pressure liquid chromatography eluting with 30:70:0.1, by volume, acetonitrile : water : trifluoroacetic acid to afford (3-[(2*S*)-1-cyclohexylmethylsulfonyl-2-piperidyl]-1,2,4-oxadiazol-5-yl)(phenyl)methylamine as a colourless oil.

^{1}H-NMR (d_4-CH_3OH) δ : 7.50-7.30 (5H, m), 5.45 (1H, s), 5.25 (1H, s), 3.75 (1H, d), 3.30 (1H, m), 2.90 (2H, d), 2.25 (1H, d), 2.00-1.00 (18H, m).

Accurate MS : 419.2123 (MH^+).

Example 25

[5-(3-(2*S*)-1-[(Cyclohexylmethyl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)-2-furyl]methylamine



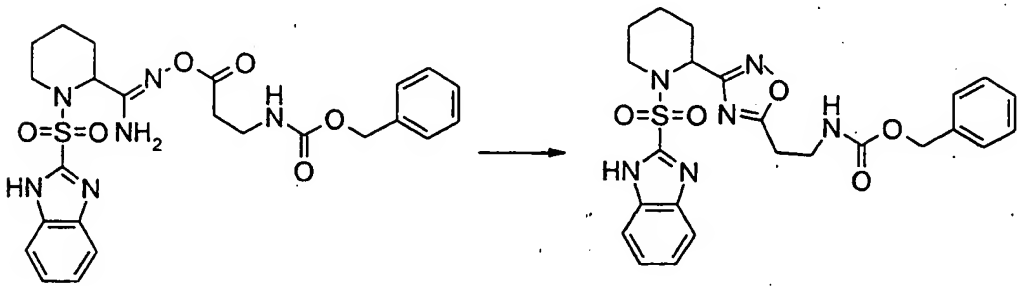
The title compound was prepared by a similar method to Example 11 from 2-[5-(3-(2*S*)-1-[(cyclohexylmethyl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)-2-furyl]methyl-1,3-isoindolinedione [see Preparation 100] and methylamine. The crude product was purified by column chromatography on silica gel eluting with 95 : 5 : 0.5, by volume, dichloromethane : methanol : 0.88 ammonia to afford [5-(3-(2*S*)-1-[(cyclohexylmethyl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)-2-furyl]methylamine as a solid.

^{1}H-NMR (d4-MeOH) δ : 7.40 (1H, d), 6.60 (1H, d), 5.30 (1H, d), 3.90 (2H, s), 3.80 (1H, d), 3.30 (1H, m), 3.05 (2H, m), 2.30 (1H, d), 2.00-1.90 (4H, m), 1.80-1.60 (7H, m), 1.40-1.00 (5H, m).

Accurate MS : Found 409.1928 (MH^+). $C_{19}H_{28}N_4O_4S$ requires 409.1910 (MH^+).

Example 26

Benzyl *N*-(2-(3-[1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-yl)ethyl)carbamate



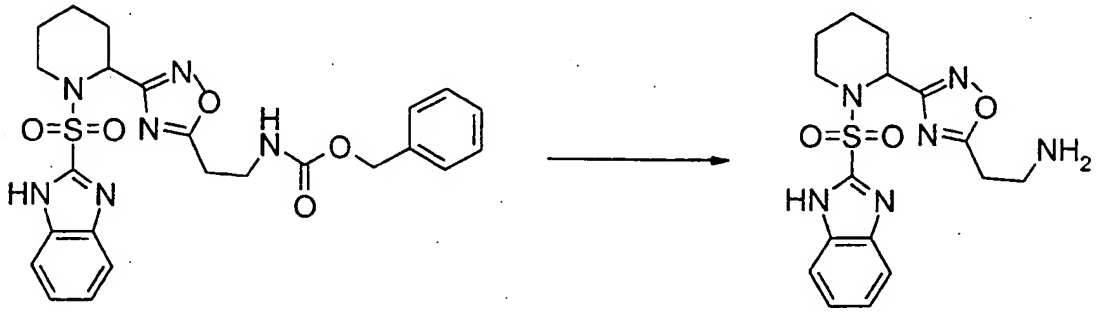
The title compound was prepared by a similar method to Example 16 from the compound of Preparation 37 and pyridine. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 70:30 changing to 60:40, by volume, hexane : ethyl acetate to afford benzyl *N*-(2-(3-[1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-yl)ethyl)carbamate as a colourless oil.

^{1}H-NMR (d_6-DMSO) δ : 13.60 (1H, bs), 7.80 (1H, bs), 7.60 (1H, bs), 7.30 (7H, m), 5.40 (1H, d), 5.00 (2H, s), 3.90 (2H, d), 3.40 (1H, d), 3.20 (2H, t), 2.75 (2H, m), 2.00 (1H, d), 1.80 (1H, m), 1.60 (1H, d), 1.50-1.20 (2H, m).

Analysis : Found C, 55.48; H, 5.22; N, 15.57; $C_{24}H_{26}N_6O_5S$. 0.1EtOAc. 0.5 H_2O requires C, 55.46; H, 5.30; N, 15.90%. (EtOAc = ethyl acetate).

Exampl 27

2-(3-[1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-yl)ethylamine



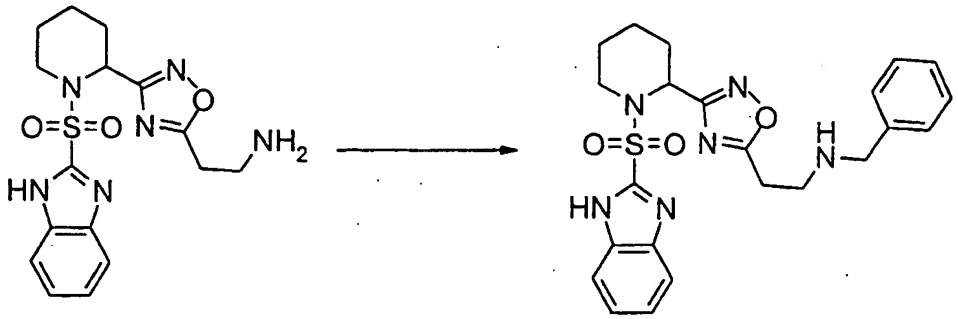
Benzyl *N*-(2-(3-[1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-yl)ethyl)carbamate (1.88g) [see Example 26] was dissolved in 45% w/w hydrogen bromide in glacial acetic acid (30ml). The reaction mixture was stirred at room temperature for 3.5 hours after which time the mixture was diluted with water and washed with diethyl ether. The aqueous layer was then basified with potassium carbonate and then extracted with ethyl acetate. The organic layer was dried over magnesium sulphate, and the solution was left to stand for 18 hours after which time a solid had formed. This was filtered off to afford 2-(3-[1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-yl)ethylamine (0.71g) as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 11.50 (1H, s), 7.80 (4H, d), 5.60 (1H, s), 4.00 (1H, d), 3.80 (2H, d), 3.45 (3H, m), 3.30 (1H, m), 2.60 (1H, d), 2.20 (1H, m), 1.90-1.60 (3H, m), 1.40 (1H, m).

Analysis : Found C, 48.93; H, 5.25; N, 21.09; $C_{16}H_{20}N_6SO_3$. 0.9 H_2O requires C, 48.94; H, 5.60; N, 21.40%.

Example 28

N-(2-(3-[1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-yl)ethyl)benzylamine



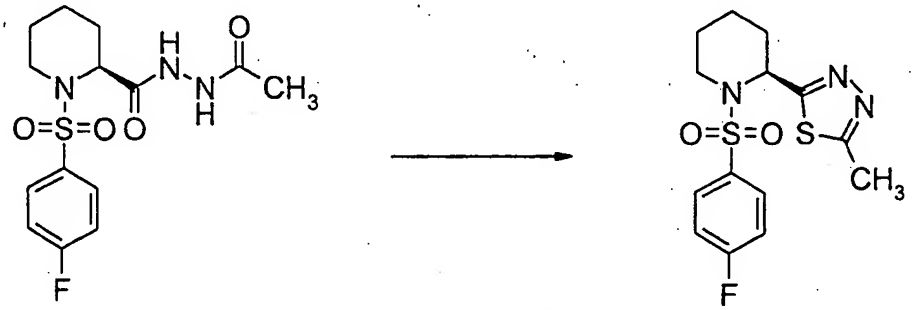
The title compound was prepared by a similar method to Example 13 from 2-(3-[1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-yl)ethylamine [see Example 27] and benzaldehyde. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 99:1 changing to 98:2, by volume, dichloromethane : methanol to afford *N*-(2-(3-[1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-yl)ethyl)-benzylamine.

^{1}H-NMR (d_4-CH_3OH) δ : 7.60 (2H, d), 7.40-7.20 (7H, m), 5.45 (1H, d), 4.10 (1H, d), 3.60 (2H, s), 3.40 (1H, t), 2.60 (4H, m), 2.10 (1H, d), 2.00 (1H, m), 1.70 (1H, m), 1.50 (3H, m).

Analysis : Found C, 57.42; H, 5.61; N, 17.43; $C_{23}H_{26}N_6O_3S.0.8\ H_2O$ requires C, 57.44; H, 5.78; N, 17.47%.

Example 29

2-[(2*S*)-1-[(4-Fluorophenyl)sulfonyl]-2-piperidyl]-5-methyl-1,3,4-thiadiazole



Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide] (271mg) was added to a solution of *N*'2-acetyl-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarbohydrazide (192mg) [see Preparation 39] in toluene (10ml). The reaction mixture was heated under reflux for 3 hours and the cooled mixture was then purified by column chromatography on silica gel eluting with a solvent gradient of 0:100 changing to 30:70 (in 10% increments), by volume, hexane : ethyl acetate, to afford 2-[(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidyl]-5-methyl-1,3,4-thiadiazole (106mg) as a clear oil.

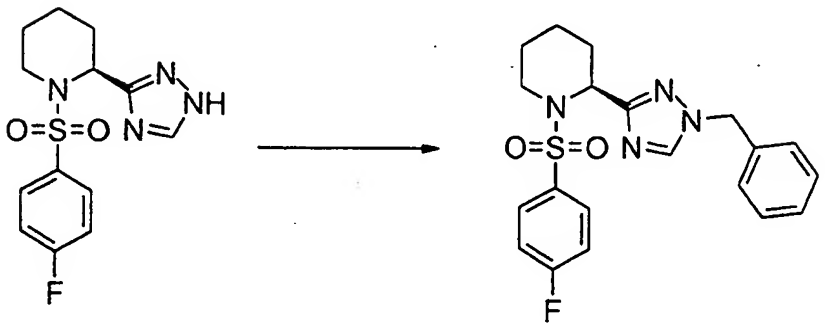
^{1}H-NMR ($CDCl_3$) δ : 7.85 (2H, m), 7.20 (2H, m), 5.60 (1H, s), 3.90 (1H, d), 3.20 (1H, t), 2.80 (3H, s), 2.40 (1H, d), 1.80-1.40 (5H, m).

Analysis : Found C, 48.07; H, 4.63; N, 11.60; $C_{14}H_{16}N_3O_2S.0.5\ H_2O$ requires C, 47.98; H, 4.89; N, 11.99%.

Rotation : $[\alpha]_D$ = -64.01°. (c = 0.1, methanol).

Exampl 30

(2*S*)-2-(1-Benzyl-1*H*-1,2,4-triazol-3-yl)-1-[(4-fluorophenyl)sulfonyl]piperidine



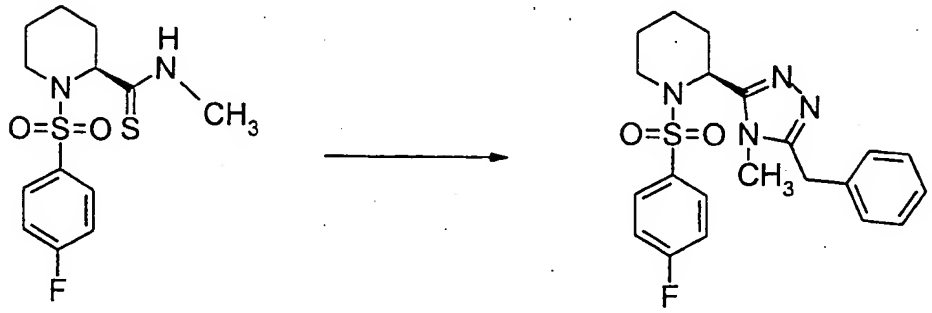
Benzyl bromide (40µl) was added to a solution of (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-(1*H*-1,2,4-triazol-3-yl)piperidine (95mg) [see Preparation 42] and potassium carbonate (47mg) in dimethylformamide (5ml). The reaction mixture was stirred at 50°C for 7 hours, after which time the solvent was removed under reduced pressure and the residue diluted with ethyl acetate. The organic solution was washed with water, dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with 100:0 changing to 50:50, by volume, hexane : ethyl acetate (in 10% increments), to afford (2*S*)-2-(1-benzyl-1*H*-1,2,4-triazol-3-yl)-1-[(4-fluorophenyl) sulfonyl]piperidine (35mg) as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 7.70 (1H, s), 7.60 (2H, t), 7.40 (2H, d), 7.20 (3H, m), 6.80 (2H, t), 5.40 (1H, s), 5.10 (2H, s), 3.80 (1H, d), 3.40 (1H, t), 2.05 (1H, m), 1.90 (1H, m), 1.70-1.50 (4H, m).

Analysis : Found C, 59.42; H, 5.25; N, 13.66; $C_{20}H_{21}N_4O_2S.0.05\ CH_2Cl_2$ requires C, 59.50; H, 5.25; N, 13.84%.

Exampl 31

(2*S*)-2-(5-Benzyl-4-methyl-4*H*-1,2,4-triazol-3-yl)-1-[(4-fluorophenyl)sulfonyl]piperidine



Phenylacetic hydrazide (180mg) was added to a solution of *N*2-methyl-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarbothioamide (270mg) [see Preparation 44] and mercuric oxide (202mg) in 1,4-dioxane (10ml). The reaction mixture was heated under reflux and stirred for 18 hours. The dioxane was then removed under reduced pressure and dimethylacetamide (10ml) added followed by phenylacetic hydrazide (180mg) and mercuric oxide (202mg). The reaction mixture was heated to 140°C and stirred for 18 hours. After this time the solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The organic layer was separated and washed with 1N aqueous hydrochloric acid solution, dried over magnesium sulphate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 100:0 changing to 0:100, by volume, hexane:ethyl acetate (in 10% increments). The product was further purified on a MCI (trade mark) reverse phase gel column eluting with a solvent gradient of 50:50 changing to 0:100 (in 5% increments), by volume, water : methanol. This gave (2*S*)-2-(5-benzyl-4-methyl-4*H*-1,2,4-triazol-3-yl)-1-[(4-fluorophenyl)sulfonyl]piperidine (57mg) as a yellow solid.

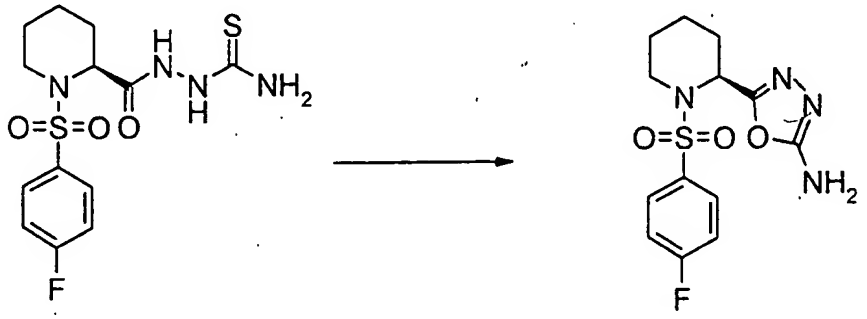
^{1}H-NMR ($CDCl_3$) δ : 7.60 (2H, d), 7.30 (2H, m), 7.25 (1H, m), 7.20 (2H, d). 7.10 (2H, t), 5.10 (1H, s), 4.10 (2H, s), 3.60 (1H, d), 3.50 (3H, s), 3.40 (1H, t), 2.25 (1H, m), 2.00 (1H, d), 1.75 (1H, m), 1.50 (2H, m), 1.25 (1H, m).

Rotation : $[\alpha]_D^{25}$ = 0.21° (c = 0.1, methanol).

Analysis : Found C, 60.44; H, 5.56; N, 13.33; $C_{21}H_{23}FN_4O_2S$ requires C, 60.85; H, 5.59; N, 13.52%.

Example 32

2-Amino-5-[(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidyl]-1,3,4-oxadiazole



Mercuric oxide (204mg) was added to a solution of 2-((2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidylcarbonyl)-1-hydrazinecarbothioamide (170mg) [see Preparation 45] in 1,4-dioxane (5ml). The reaction mixture was heated under reflux and stirred for 4 hours. The resulting suspension was filtered through a plug of ARBOCEL (trade mark) filter aid, washing with dichloromethane:methanol (90:10, by volume). The filtrate was evaporated under reduced pressure and purified by column chromatography on silica gel eluting with 100:0 changing to 90:10 (in 5% increments), by volume,

dichloromethane:methanol. The product was further purified by column chromatography on silica gel eluting with 0:100 changing to 60:40, by volume, ethyl acetate:hexane, to afford 2-amino-5-[(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidyl]-1,3,4-oxadiazole (64mg) as a white solid.

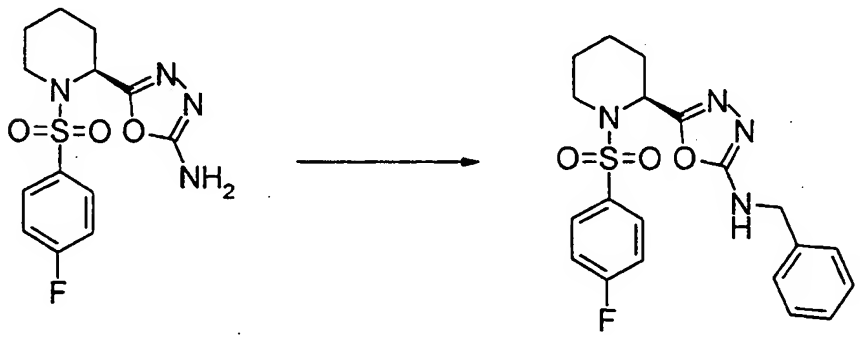
^{1}H-NMR ($CDCl_3$) δ : 7.80 (2H, m), 7.10 (2H, m), 5.30 (1H, s), 5.00 (2H, s), 3.80 (1H, d), 3.10 (1H, t), 2.10 (1H, d), 1.90-1.60 (5H, m).

Rotation : $[\alpha]_D^{25}$ = -39.21° (c = 0.1, methanol).

Analysis : Found C, 47.49; H, 4.59; N, 16.79; $C_{13}H_{15}FN_4O_3S.0.2\ H_2O$ requires C, 47.32; H, 4.70; N, 16.98%.

Example 33

2-Benzylamino-5-[(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidyl]-1,3,4-oxadiazole



Benzaldehyde (101μl) was added to a solution of 2-amino-5-[(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidyl]-1,3,4-oxadiazole (163mg) [see Example 32] in tetrahydrofuran (2ml), followed by acetic acid (172μl) and sodium triacetoxyborohydride (297mg). The reaction mixture was stirred at room temperature for 18 hours, after which time the solvent was removed under reduced pressure and the residue partitioned between dichloromethane and

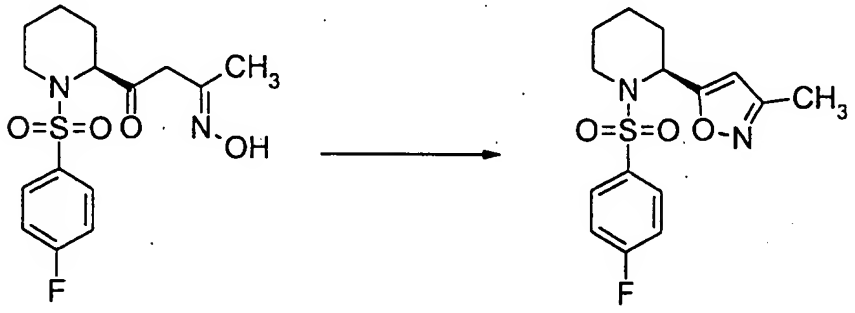
saturated aqueous sodium hydrogen carbonate solution. The organic layer was separated, dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 0:100 changing to 40:60 (in 10% increments), by volume, ethyl acetate:hexane, to afford 2-benzylamino-5-[(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidyl]-1,3,4-oxadiazole (6mg) as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 7.80 (2H, m), 7.35 (5H, m), 7.05 (2H, t), 5.25 (1H, s), 5.00 (1H, s), 4.40 (2H, s), 3.70 (1H, d), 3.10 (1H, t), 2.05 (1H, t), 1.80 (1H, m), 1.50-1.35 (4H, m).

MS : 417(MH^+).

Example 34

5-[(2*S*)-1-[(4-Fluorophenyl)sulfonyl]-2-piperidyl]-3-methylisoxazole



Mesyl chloride (57μl) was added to a solution of the compound of Preparation 47 (211 mg) and triethylamine (111μl) in dichloromethane (4ml) at 0°C. The reaction mixture was stirred at room temperature for 18 hours. After this time the mixture was purified by column chromatography on silica gel eluting with a

solvent gradient of 0:100 changing to 10:90 (in 5% increments), by volume, ethyl acetate:hexane. The product was further purified by column chromatography on silica gel as above to afford 5-[(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidyl]-3-methylisoxazole (26mg) as a clear oil.

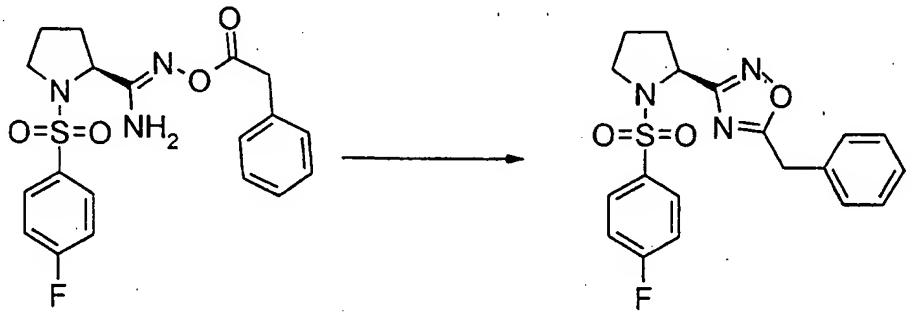
^{1}H-NMR ($CDCl_3$) δ : 7.80 (2H, t), 7.10 (2H, t), 5.80 (1H, s), 5.30 (1H, d), 3.75 (1H, d), 3.05 (1H, t), 2.20 (3H, s), 2.10 (1H, d), 1.80 (1H, m), 1.60 (2H, m), 1.40 (2H, m).

Rotation : $[\alpha]_D^{25}$ = - 49.61° (c = 0.1, methanol).

MS : 325 (MH^+).

Example 35

5-Benzyl-3-[(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-pyrrolidyl]-1,2,4-oxadiazole



The title compound was prepared by a similar method to Preparation 6 from the compound of Preparation 53 and xylene. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 0:100 changing to 30:70, by volume, ethyl acetate : hexane. This gave 5-benzyl-3-[(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-pyrrolidyl]-1,2,4-oxadiazole as a colourless oil.

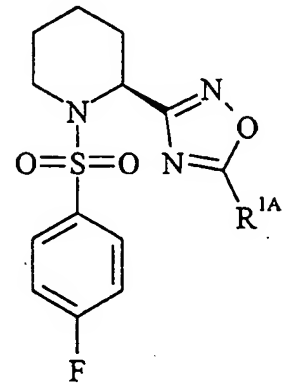
^{1}H-NMR ($CDCl_3$) δ : 7.80 (2H, t), 7.40 (5H, m), 7.05 (2H, t), 5.00 (1H, d), 4.15 (2H, s), 3.50 (2H, m), 2.20 (3H, m), 1.90 (1H, m).

Rotation : $[\alpha]_D^{25}$ = -100.22° (c = 0.1, methanol).

Analysis : Found C, 58.24; H, 4.65; N, 10.64; $C_{19}H_{18}N_3FO_3S.0.05\ CH_2Cl_2$ requires C, 58.42; H, 4.66; N, 10.73%.

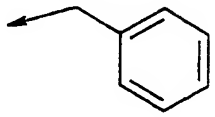
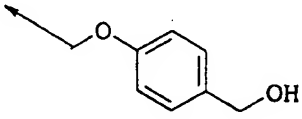
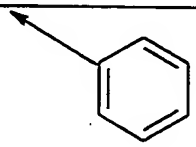
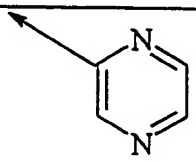
Example 36 to 39

The compounds of the following tabulated Examples (Table 3) of the general formula:



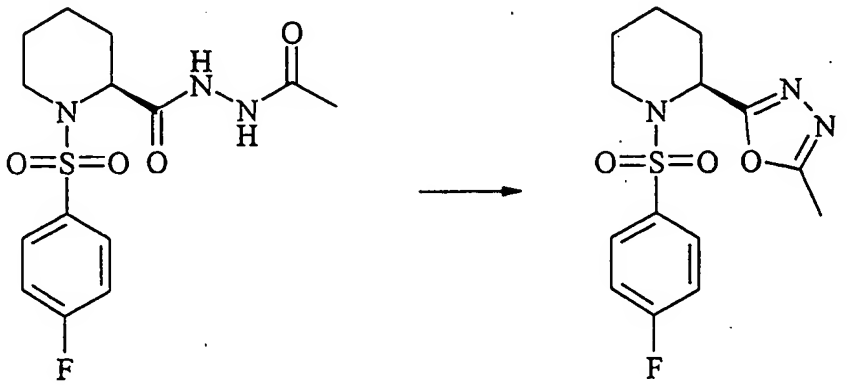
were prepared by a similar method to Preparation 6, either from the corresponding hydroxyamidine derivative and xylene (Examples 36,38) or from the corresponding hydroxyamidine derivative and pyridine (Examples 37,39).

Table 3

Example No.	Starting material prep. No.	R^{1A}	Analytical data
36	74		^{1}H-NMR ($CDCl_3$) δ : 7.70 (2H, m), 7.40-7.20 (5H, m), 6.90 (2H, t), 5,40 (1H, d), 4.10 (2H, s), 3.80 (1H, d), 3.30 (1H, t), 2.00 (2H, m), 1.80-1.60 (4H, m). Analysis : Found C, 59.72; H, 4.83; N, 10.34; $C_{20}H_{20}N_3O_3SF$ requires C, 59.84; H, 5.02; N, 10.47%.
37	75		^{1}H-NMR ($CDCl_3$) δ : 7.70 (2H, m), 7.30 (2H, d), 7.00 (2H, t), 6.95 (2H, d), 5.40 (1H, d), 5.15 (2H, s), 4.60 (2H, d), 3.80 (1H, d), 3.25 (1H, t), 2.10 (1H, m), 2.00 (1H, m), 1.70-1.40 (4H, m). Analysis : Found C, 55.22; H, 4.88; N, 8.98; $C_{21}H_{22}N_3O_5SF.0.5\ H_2O$ requires C, 55.25; H, 5.08; N, 9.20%.
38	76		^{1}H-NMR ($CDCl_3$) δ : 8.00 (2H, d), 7.75 (2H, m), 7.55 (1H, m), 7.50 (2H, m), 7.00 (2H, m), 5.45 (1H, d), 3.80 (1H, d), 3.40 (1H, t), 2.20 (1H, d), 2.00 (1H, m), 1.80-1.50 (4H, m). Analysis : Found C, 58.87; H, 4.60; N, 10.72; $C_{19}H_{18}N_3O_3SF$ requires C, 58.90; H, 4.68; N, 10.85%. Rotation : $[\alpha]_D$ = -33.21°(c = 0.1, methanol).
39	97		^{1}H-NMR ($CDCl_3$) δ : 9.25 (1H, s), 8.80 (2H, m), 7.80 (2H, m), 7.00 (2H, m), 5.50 (1H, d), 3.85 (1H, d), 3.40 (1H, t), 2.20 (1H, d), 2.00 (1H, m), 1.80-1.40 (4H, m). Analysis : Found C, 52.50; H, 4.09; N, 17.85; $C_{17}H_{16}N_5O_3SF$ requires C, 52.44; H, 4.14; N, 17.98%. Rotation : $[\alpha]_D$ = -55.61° (c = 0.1, methanol).

Example 40

2-(1*S*)-2-[(4-Fluorophenyl)sulfonyl]cyclohexyl-5-methyl-1,3,4-oxadiazole



Iodine (239mg) was added to a stirred solution of triphenylphosphine (247mg) in dichloromethane (6ml) at room temperature under an atmosphere of nitrogen. The reaction mixture was stirred for 10mins, then triethylamine (0.269ml) was added followed by *N*'2-acetyl-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarbohydrazide (160mg) [see Preparation 39] in dichloromethane (2ml). The reaction mixture was stirred for 18hrs, after which time the solvent was removed under reduced pressure. The crude product was pre-absorbed onto silica gel and purified by column chromatography on silica gel eluting with a solvent gradient of 0:100 changing to 30:70, by volume, ethyl acetate : hexane, to afford 2-(1*S*)-2-[(4-fluorophenyl)sulfonyl]cyclohexyl-5-methyl-1,3,4-oxadiazole (87mg) as an oil.

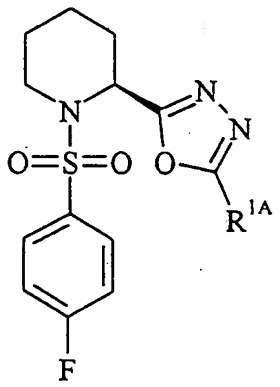
^{1}H-NMR ($CDCl_3$) δ : 7.80 (2H, m), 7.20 (2H, m), 5.40 (1H, m), 3.80 (1H, d), 3.20 (1H, t), 2.40 (3H, s), 2.15 (1H, d), 2.00 (1H, m), 1.80-1.50 (4H, m).

Analysis : Found C, 51.52; H, 4.97; N, 12.57; $C_{14}H_{16}N_3O_3SF$ requires C, 51.68; H, 4.96; N, 12.91%.

Rotation : $[\alpha]_D^{25}$ = -71.41° (c = 0.1, methanol).

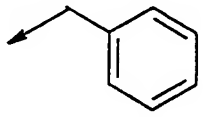
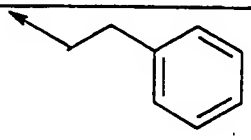
Examples 41 and 42

The compounds of the following tabulated Examples (Table 4) of the general formula :



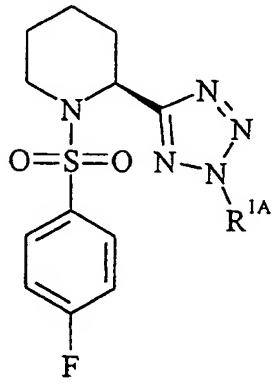
were prepared by a similar method to Example 40 from the corresponding hydrazide, iodine, triphenylphosphine and triethylamine.

Table 4

Example No.	Starting material prep. No.	R^{1A}	Analytical data
41	77		^{1}H-NMR ($CDCl_3$) δ : 7.75 (2H, m), 7.45-7.20 (5H, m), 7.00 (2H, t), 5.40 (1H, d), 4.10 (2H, d), 3.80 (1H, d), 3.20 (1H, t), 2.20-1.90 (2H, m), 1.80-1.50 (4H, m), Analysis : Found C, 58.43; H, 4.98; N, 10.06; $C_{20}H_{20}N_3O_3SF.0.15$ CH_2Cl_2 requires C, 58.43; H, 4.94; N, 10.14%. Rotation : $[\alpha]_D$ = -42.01° (c = 0.1, methanol).
42	78		^{1}H-NMR ($CDCl_3$) δ : 7.75 (2H, m), 7.30-7.10 (7H, m), 5.40 (1H, s), 3.80 (1H, d), 3.20-3.00 (5H, m), 2.10 (1H, d), 2.00 (1H, m), 1.70-1.50 (4H, m). Analysis : Found C, 58.40; H, 5.18; N, 9.57; $C_{21}H_{22}N_3O_3SF.0.1CH_2Cl_2.0.5H_2O$ requires C, 58.53; H, 5.40; N, 9.70%. Rotation : $[\alpha]_D$ = -49.41° (c = 0.1, methanol).

Examples 43 and 44

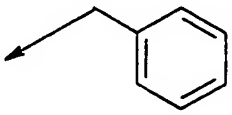
The compounds of the following tabulated Examples (Table 5) of the general formula:



were prepared by a similar method to Example 30. Example 43 was prepared from (2*S*)-1-[(4-Fluorophenyl)sulfonyl]-2-(2*H*-1,2,3,4-tetraazol-5-yl)piperidine [see Preparation 79] and benzyl bromide. Example 44 was prepared from (2*S*)-1-[(4-Fluorophenyl)sulfonyl]-2-(2*H*-1,2,3,4-tetraazol-5-yl)piperidine [see Preparation 79] and methyl iodide.

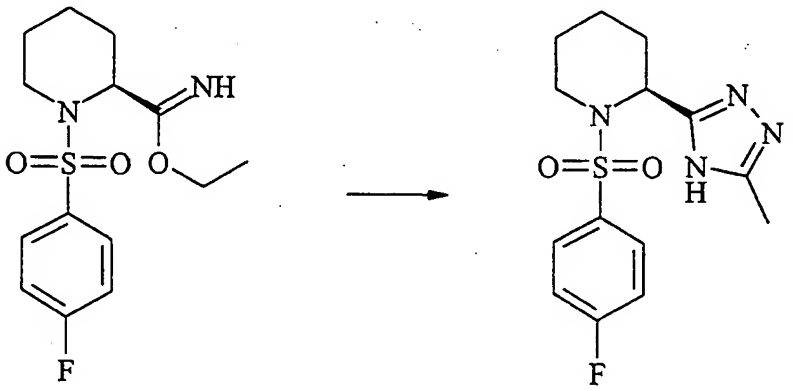
Purification of both Examples was achieved by chromatography on silica, eluting with 100:0, changing to 75:25, by volume, ethyl acetate:hexane, with desired product isolated as the less polar regioisomer

Table 5

Example No.	Starting material prep. No.	R_{1A}	Analytical data
43	79		^{1}H-NMR ($CDCl_3$) δ : 7.60 (2H, m), 7.40-7.30 (5H, m), 6.80 (2H, t), 5.60 (3H, m), 3.85 (1H, d), 3.35 (1H, t), 2.05 (2H, m), 1.80-1.60 (4H, m). Analysis : Found C, 56.64; H, 4.98; N, 17.34; $C_{19}H_{20}N_5O_2SF$ requires C, 56.84; H, 5.02; N, 17.44%. Rotation : $[\alpha]_D$ = -37.3° (c = 0.1, methanol).
44	79	CH_3	^{1}H-NMR ($CDCl_3$) δ : 7.70 (2H, m), 7.05 (2H, t), 5.60 (1H, s), 4.20 (3H, s), 3.85 (1H, d), 3.35 (1H, t), 2.05 (2H, m), 1.80-1.60 (4H, m). Analysis : Found C, 47.69; H, 4.89; N, 21.27; $C_{13}H_{16}N_5O_2SF$ requires C, 47.99; H, 4.96; N, 21.52%. Rotation : $[\alpha]_D$ = -54.34° (c = 0.1, methanol).

Example 45

(2*S*)-1-[(4-Fluorophenyl)sulfonyl]-2-(5-methyl-4*H*-1,2,4-triazol-3-yl)piperidine



Acetyl chloride (91ml) was added to a stirred solution of ethyl (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboximidate (288mg) [see Preparation 41] and triethylamine (178ml) in toluene (5ml). The reaction mixture was stirred at room temperature for 1hr after which time hydrazine hydrate (62ml) was added. The mixture was stirred for 18hrs and then poured into a column containing silica gel, and the product eluted with a solvent gradient of 1:1, by volume, ethyl acetate : hexane followed by 95:5 ethyl acetate : methanol. The fractions containing the product were combined and the solvent removed under reduced pressure, the remaining residue was dissolved in toluene (10ml) and the reaction mixture was heated to reflux for 1hr. Tosic acid (5mg) was then added and the mixture was heated to reflux for a further 18hrs. The cooled reaction

mixture was then purified by column chromatography on silica gel eluting with a solvent gradient of 1:1, changing to 0:100, by volume, hexane : ethyl acetate, in 10% increments, to afford (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-(5-methyl-4*H*-1,2,4-triazol-3-yl)piperidine (60mg) as a white solid.

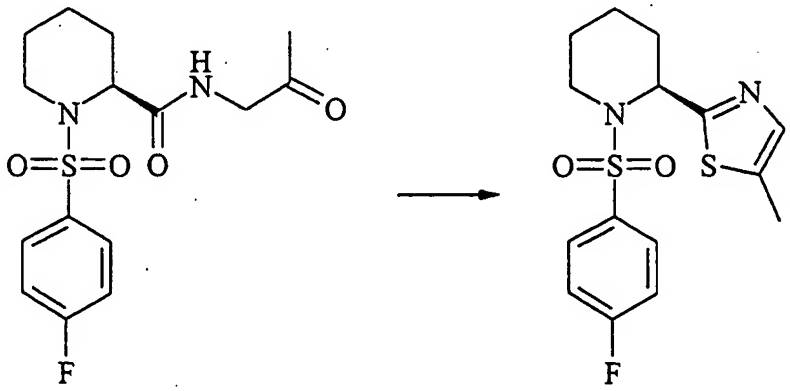
^{1}H-NMR ($CDCl_3$) δ : 7.80 (2H, m), 7.15 (2H, t), 5.30 (1H, s), 3.80 (1H, d), 3.30 (1H, bs), 2.40 (3H, s), 2.30 (1H, d), 1.80 (1H, bs), 1.50 (3H, m), 1.45 (1H, m).

Analysis : Found C, 51.53; H, 5.25; N, 17.15; $C_{14}H_{17}N_4O_2SF$ requires C, 51.84; H, 5.28; N, 17.27%.

Rotation : $[\alpha]_D^{25}$ = -136.76° (c = 1.0, methanol).

Example 46

(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-(5-methyl-1,3-thiazol-2-yl)piperidine



The title compound was prepared by a similar method to Example 29 from (2*S*)-1-[(4-fluorophenyl)sulfonyl]-*N*^{2}-(2-oxopropyl)-2-piperidinecarboxamide [see Preparation 81] and Lawesson's reagent. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 100:0 changing to 75:25, by volume, hexane : ethyl acetate, in 5% increments, to afford (2S)-1-[(4-fluorophenyl)sulfonyl]-2-(5-methyl-1,3-thiazol-2-yl)piperidine as a white solid.

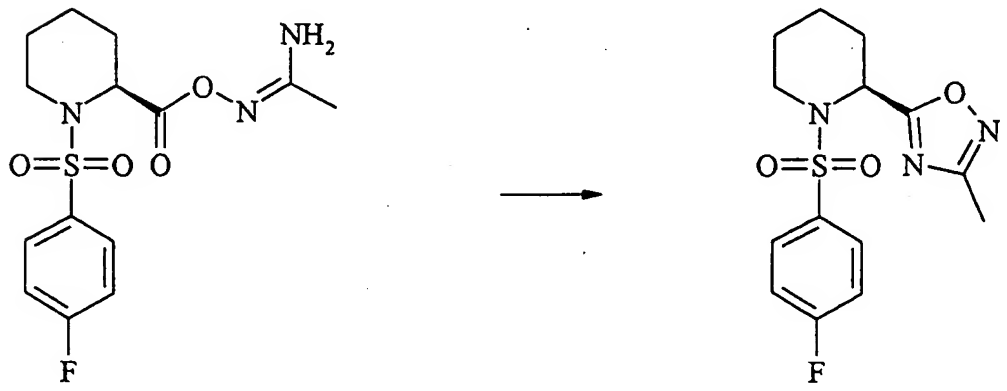
^{1}H-NMR ($CDCl_3$) δ : 7.85 (2H, m), 7.25 (1H, s), 7.20 (2H, t), 5.40 (1H, d), 3.90 (1H, d), 3.25 (1H, t), 2.45 (3H, s), 2.40 (1H, d), 1.80 (1H, m), 1.60 (3H, m), 1.40 (1H, m).

Analysis : Found C, 52.78; H, 5.03; N, 8.12; $C_{15}H_{17}N_2O_2S_2F$ requires C, 52.92; H, 5.03; N, 8.23%.

Rotation : $[\alpha]_D^{25}$ = -47.32° (c = 0.1, methanol).

Exampl 47

(2*S*)-1-[(4-Fluorophenyl)sulfonyl]-2-(3-methyl-1,2,4-oxadiazol-5-yl)piperidine



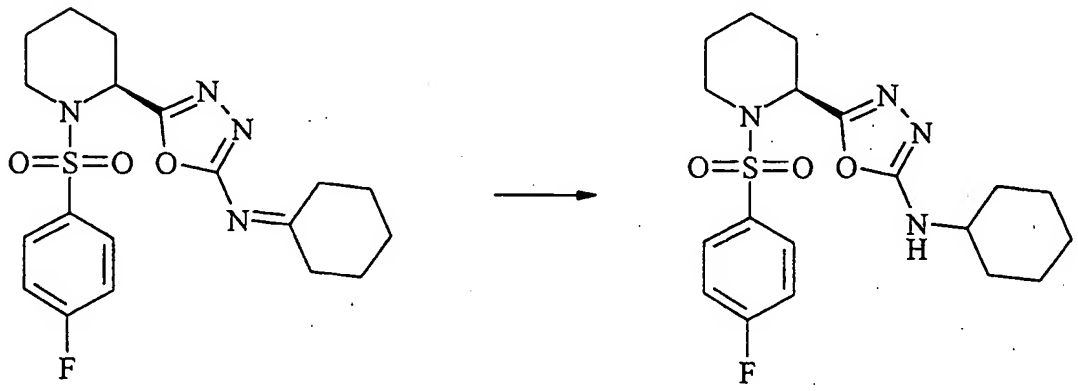
The title compound was prepared by a similar method to Preparation 6 from *N*^{1}-[((2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidylcarbonyl)oxy]ethanimidamide [see Preparation 82] and xylene. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 100:0 changing to 80:20, by volume, hexane : ethyl acetate in 10% increments, to afford (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-(3-methyl-1,2,4-oxadiazol-5-yl)piperidine as an oil.

^{1}H-NMR ($CDCl_3$) δ : 7.75 (2H, m), 7.10 (2H, t), 5.50 (1H, d), 3.85 (1H, d), 3.30 (1H, t), 2.25 (3H, s), 2.05 (2H, m), 1.80-1.60 (3H, m), 1.50 (1H, m).
Analysis : Found C, 51.30; H, 4.89; N, 12.38; $C_{14}H_{16}N_3O_3SF.0.25H_2O$ requires C, 50.98; H, 5.04; N, 12.74%.

Rotation : $[\alpha]_D^{25}$ = -71.01° (c = 0.1, methanol).

Example 48

N^2-Cyclohexyl-5-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidyl-1,3,4-oxadiazol-2-amine



Sodium borohydride (71mg) was added to a stirred solution of N^2-cyclohexyliden-5-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidyl-1,3,4-oxadiazol-2-amine [see Preparation 83] in ethanol (15ml) and methanol (5ml). The reaction mixture was stirred for 3hrs after which time further sodium borohydride (30mg) was added to the mixture. The mixture was stirred for a further 18hrs and then the solvent was removed under reduced pressure, the residue was partitioned between dichloromethane and 1N aqueous hydrochloric acid. The aqueous layer was separated and basified to pH 8 with 0.88 aqueous ammonia, the product was re-extracted with dichloromethane, dried over magnesium sulphate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 100:0 changing to 50:50, by volume, hexane : ethyl acetate,

in 5% increments, to afford N^2-cyclohexyl-5-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidyl-1,3,4-oxadiazol-2-amine (59mg) as a white gum.

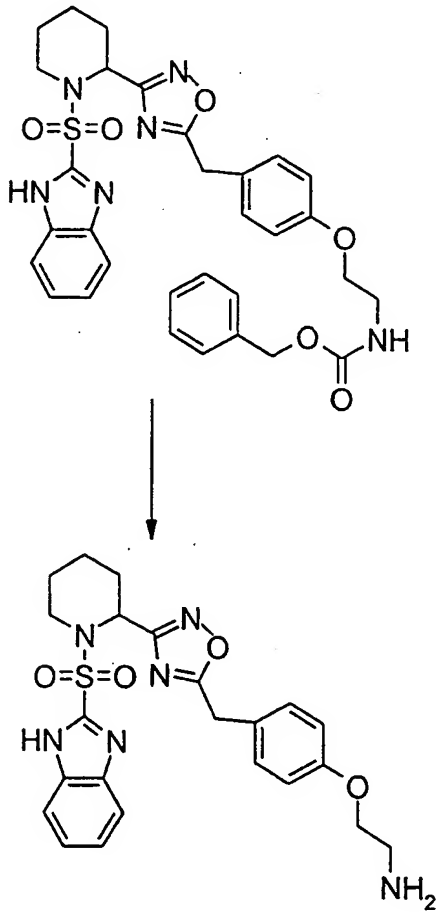
^{1}H-NMR ($CDCl_3$) δ : 7.75 (2H, m), 7.10 (2H, t), 5.25 (1H, d), 4.30 (1H, d), 3.75 (1H, d), 3.40 (1H, m), 3.10 (1H, t), 2.00 (3H, m), 1.85 (1H, m), 1.70-1.60 (5H, m), 1.40 (2H, m), 1.25 (4H, m), 0.95 (1H, m).

Analysis : Found C, 55.28; H, 6.35; N, 12.22; $C_{19}H_{25}N_4O_3SF$ 0.3 hexane. H_2O requires C, 55.52; H, 6.45; N, 12.45%.

Rotation : $[\alpha]_D^{25}$ = -13.00° (c = 0.1, methanol).

Example 49

2-[4-(3-[1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethyl)phenoxy]ethylamine



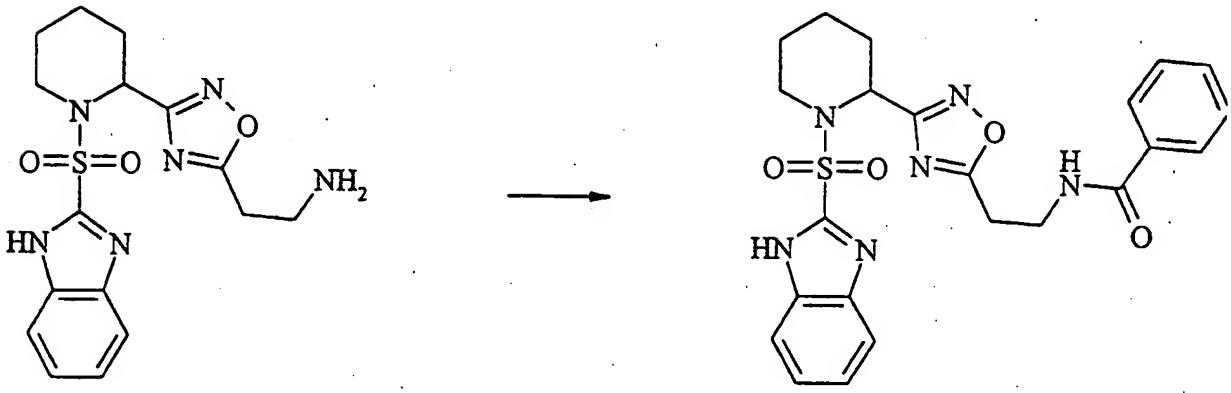
The title compound was prepared by a similar method to Example 27 from benzyl *N*-(2-[4-(3-[1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethyl)phenoxy]ethyl)carbamate [see Preparation 56] and 45% w/w hydrogen bromide in glacial acetic acid to afford 2-[4-(3-[1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethyl)phenoxy]ethylamine as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 7.40 (2H, m), 7.25 (2H, m), 7.10 (2H, d), 6.85 (2H, d), 5.55 (1H, d), 4.00 (3H, m), 3.90 (2H, s), 3.20 (1H, m), 3.10 (2H, m), 2.30 (1H, d), 2.10 (1H, m), 1.80-1.40 (7H, m).

Analysis : Found C, 55.33; H, 5.49; N, 15.84; $C_{23}H_{26}N_6O_4S$. 0.6 EtOAc. 0.7 H_2O requires C, 55.67; H, 5.92; N, 15.33%. (EtOAc = ethyl acetate).

Example 50

N^1-(2-3-[1-(1*H*-Benzo[d]imidazol-2-ylsulfonyl)-2-piperidinyl]-1,2,4-oxadiazol-5-ylethyl)benzamide



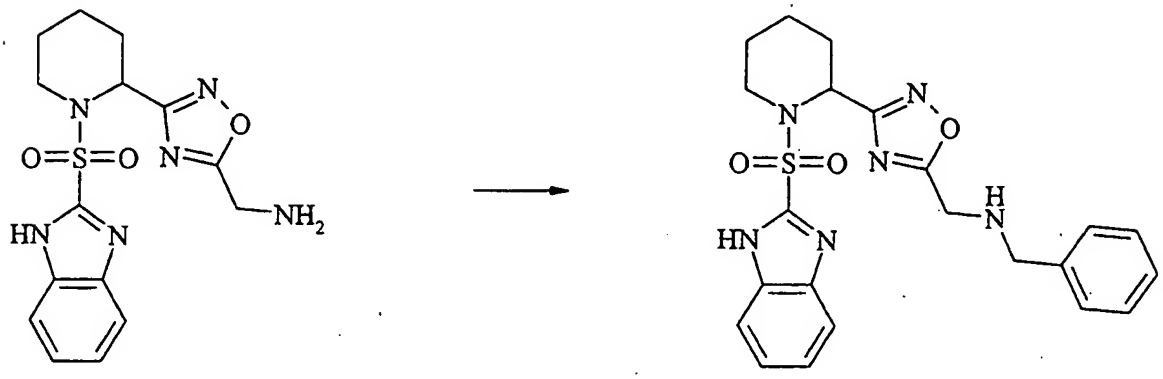
Benzoyl chloride (0.07ml) was added to a solution of 2-3-[1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylethylamine (0.2g) [see Example 27] and triethylamine (0.11ml) in dichloromethane (5ml). The reaction mixture was stirred at room temperature for 18hrs, after which time a white solid was filtered off, and the filtrate concentrated under reduced pressure. The remaining residue was dissolved in ethyl acetate and washed with water and 1N aqueous hydrochloric acid. The organic layer was then dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with 1 :1, by volume, ethyl acetate : hexane, to afford *N*^{1}-(2-3-[1-(1*H*-benzo[d]imidazol-2-ylsulfonyl)-2-piperidinyl]-1,2,4-oxadiazol-5-ylethyl)benzamide (63mg) as a white solid.

^{1}H-NMR (d6-DMSO) δ : 13.60 (1H, bs), 8.60 (1H, bs), 7.80 (2H, d), 7.70 (2H, m), 7.60-7.20 (5H, m), 5.40 (1H, m), 3.90 (1H, d), 3.50 (2H, m), 3.30 (1H, m), 2.90 (2H, m), 2.00 (1H, m), 1.80 (1H, m), 1.50 (1H, d), 1.40 (1H, m), 1.35-1.10 (2H, m).

Analysis : Found C, 57.23; H, 5.03; N, 17.15; $C_{23}H_{24}N_6O_4S$ requires C, 57.49; H, 5.03, 17.49%.

Example 51

N-(3-[1-(1*H*-benzo[d]imidazol-2-ylsulfonyl)-2-pip ridyl]-1,2,4-oxadiazol-5-ylmethyl)-*N*-benzylamine



Benzaldehyde (0.06ml) was added to a solution of 3-[1-(1*H*-benzo[d]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethylamine (0.2g) [see Preparation 86] in tetrahydrofuran (5ml). The reaction mixture was stirred at room temperature for 30mins, after which time sodium triacetoxyborohydride (0.16g) and glacial acetic acid (0.03ml) were added, and the mixture was then stirred for 18hrs. The mixture was then diluted with water and basified with saturated sodium hydrogen carbonate, and the product was extracted with ethyl acetate. The organic layer was separated, dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 80:20

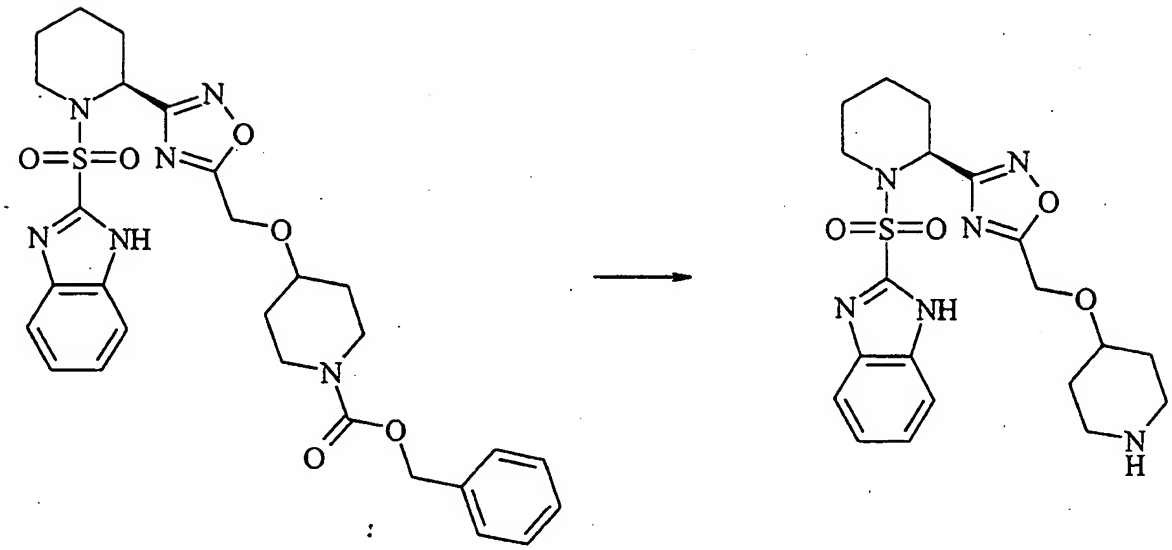
changing to 50:50, by volume, hexane : ethyl acetate, in 10% increments, to afford *N*-(3-[1-(1*H*-benzo[d]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethyl)-*N*-benzylamine (0.08g) as a white solid.

^{1}H-NMR (d6-DMSO) δ : 7.75 (1H, bs), 7.55 (1H, bs), 7.40-7.20 (9H, m), 5.40 (1H, d), 3.90 (1H, d), 3.60 (4H, m), 3.40 (1H, m), 2.00 (1H, m), 1.80 (1H, m), 1.65 (1H, m), 1.55 (1H, m), 1.40 (2H, m).

Analysis : Found C, 57.38; H, 5.45; N, 17.91; $C_{22}H_{24}N_6O_3S$ .0.5 H_2O requires C, 57.25; H, 5.46; N, 18.21%.

Example 52

2-[(2*S*)-2-5-[(4-Piperidyloxy)methyl]-1,2,4-oxadiazol-3-yl-1-piperidyl]sulfonyl-1*H*-benzo[d]imidazole



The title compound was prepared by the method of Example 27 from benzyl 4-(3-[(2*S*)-1-(1*H*-benzo[d]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-

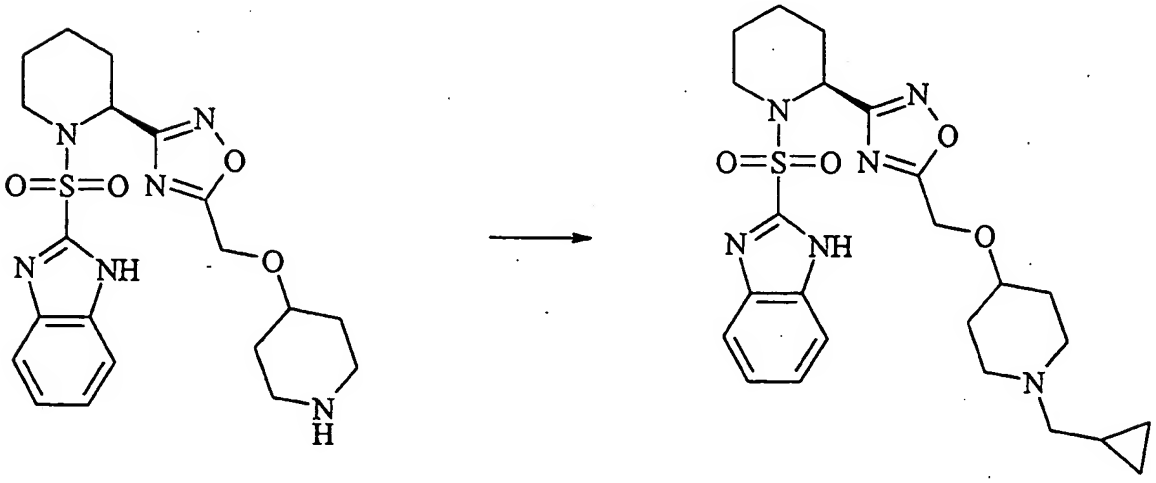
ylmethoxy)-1-piperidinecarboxylate [see Preparation 96] and hydrogen bromide in glacial acetic acid. The crude product was recrystallised from isopropanol to afford 2-[(2*S*)-2-5-[(4-piperidyloxy)methyl]-1,2,4-oxadiazol-3-yl-1-piperidyl]sulfonyl-1*H*-benzo[d]imidazole as an off-white solid.

^{1}H-NMR (d6-DMSO) δ : 7.65 (2H, m), 7.35 (2H, m), 5.40 (1H, d), 4.50 (2H, s), 3.95 (1H, d), 3.60 (1H, m), 3.35 (1H, t), 3.15 (2H, m), 2.95 (2H, m), 2.00-1.80 (4H, m), 1.75-1.30 (6H, m).

Rotation : $[\alpha]_D^{25}$ = -19.10° (c = 0.05, methanol).

Example 53

2-[(2*S*)-2-[5-([1-(Cyclopropylmethyl)-4-piperidyl]oxymethyl)-1,2,4-oxadiazol-3-yl]-1-piperidyl]sulfonyl-1*H*-benzo[d]imidazole



Cyclopropyl methyl bromide (21.4ml) was added to a solution of 2-[(2*S*)-2-5-[(4-piperidyloxy)methyl]-1,2,4-oxadiazol-3-yl-1-piperidyl]sulfonyl-1*H*-benzo[d]imidazole (100mg) [see Example 52], sodium hydrogen carbonate (18.8mg) and sodium iodide (33.6mg) in acetonitrile (2ml). The reaction mixture was stirred for 18hrs at room temperature under an atmosphere of nitrogen, after which time the mixture was diluted with ethyl acetate and water. The organic layer was separated and washed with saturated sodium hydrogen carbonate, brine, dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 98 : 1.75 : 0.25, changing to 80 : 20 : 3, by volume dichloromethane : methanol : 0.88 aqueous ammonia to afford 2-[(2*S*)-2-[5-([1-(cyclopropylmethyl)-4-piperidyl]oxymethyl)-1,2,4-oxadiazol-3-yl]-1-piperidyl]sulfonyl-1*H*-1,3-benzo[d]imidazole (35mg) as a white solid.

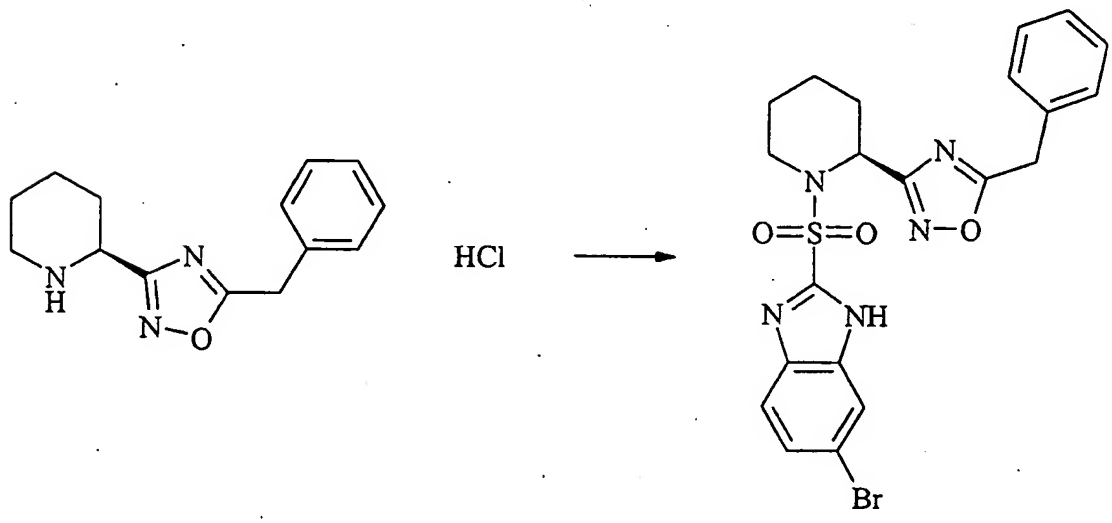
^{1}H-NMR ($CDCl_3$) δ : 7.75 (2H, m), 7.40 (2H, m), 5.60 (1H, d), 4.45 (2H, s), 3.95 (1H, d), 3.40 (1H, m), 3.15 (1H, m), 2.85 (2H, m), 2.35 (1H, d), 2.20-2.00 (4H, m), 1.90 (2H, m), 1.80-1.60 (7H, m), 0.90 (1H, m), 0.50 (2H, d), 0.10 (2H, d).

Analysis : Found C, 57.30; H, 6.54; N, 16.13; $C_{24}H_{32}N_6O_4S$. $0.5CH_3OH$ requires C, 56.96; H, 6.63; N, 16.27%.

Rotation : $[\alpha]_D^{25}$ = -52.00° (c = 0.05, methanol).

Example 54

2-[(2*S*)-2-(5-Benzyl-1,2,4-oxadiazol-3-yl)-1-piperidyl]sulfonyl-5-bromo-1*H*-benzo[d]imidazole



The title compound was prepared by a similar method to Example 1 from 5-benzyl-3-[(2*S*)-2-piperidyl]-1,2,4-oxadiazole hydrochloride [see Preparation 7] and 5-bromo-1*H*-benzo[d]imidazole-2-sulfonyl chloride [see Preparation 88]. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 90:10 changing to 70:30, by volume, hexane : ethyl acetate, in 10% increments, to afford 2-[(2*S*)-2-(5-benzyl-1,2,4-oxadiazol-3-yl)-1-piperidyl]sulfonyl-5-bromo-1*H*-benzo[d]imidazole as a white solid.

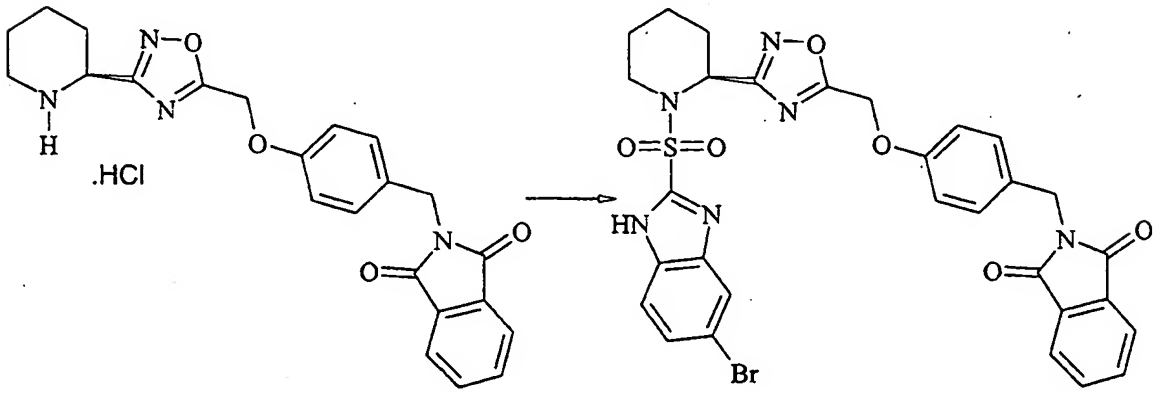
^{1}H-NMR (d6-DMSO) δ : 7.85 (1H, s), 7.60 (1H, d), 7.45 (1H, m), 7.30 (3H, m), 7.20 (2H, m), 5.35 (1H, d), 4.05 (2H, s), 3.95 (1H, d), 3.20 (1H, d), 2.00 (1H, d), 1.80 (1H, m), 1.60 (1H, d), 1.55 (1H, m), 1.40-1.20 (2H, m).

Analysis : Found C, 50.17; H, 4.16; N, 13.75; $C_{21}H_{20}N_5O_3SBr$ requires C, 50.21; H, 4.01; N, 13.94%.

Rotation : $[\alpha]_D^{25}$ = -29.41° (c = 0.1, methanol).

Example 55

2-4-[(3-(2*S*)-1-[(5-Bromo-1*H*-benzo[d]imidazol-2-yl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)methoxy]benzyl-1,3-isoindolinedione



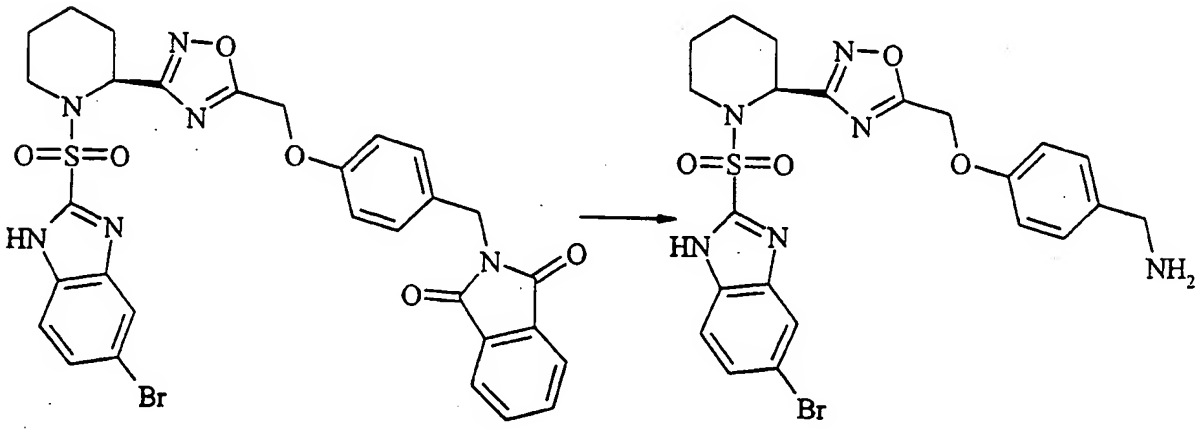
The title compound was prepared by a similar method to Example 1 from 2-[4-(3-[(2*S*)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzyl]-1,3-isoindolinedione hydrochloride [see Preparation 15] and 5-bromo-1*H*-benzo[d]imidazole-2-sulfonyl chloride [see Preparation 88]. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 90:10 changing to 40:60, by volume, hexane : ethyl acetate, in 10% increments, to afford 2-4-[(3-(2*S*)-1-[(5-bromo-1*H*-benzo[d]imidazol-2-yl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)methoxy]benzyl-1,3-isoindolinedione as a white solid.

^{1}H-NMR (d6-DMSO) δ : 7.85 (5H, m), 7.60 (1H, d), 7.40 (1H, d), 7.20 (2H, m), 6.90 (2H, d), 5.40 (1H, d), 5.20 (2H, d), 4.70 (2H, s), 3.90 (1H, d), 3.20 (1H, m), 2.00 (1H, d), 1.80 (1H, m), 1.60 (2H, m), 1.40-1.20 (2H, m).

Analysis : Found C, 52.20; H, 3.54; N, 11.92; $C_{30}H_{25}N_6O_6SBr$ $0.6H_2O$ requires C, 52.21; H, 3.86; N, 12.18%.

Example 56

4-[(3-(2*S*)-1-[(5-Bromo-1*H*-benzo[d]imidazol-2-yl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)methoxy]benzylamine



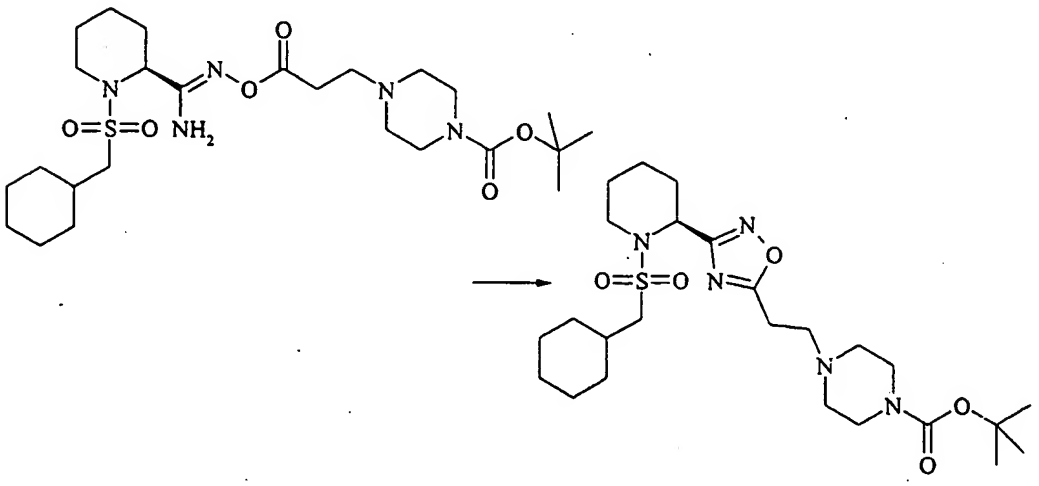
The title compound was prepared by a similar method to Example 11 from 2-4-[(3-(2*S*)-1-[(5-bromo-1*H*-benzo[d]imidazol-2-yl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)methoxy]benzyl-1,3-isoindolinedione [see Example 55] and 33% methylamine in ethanol. The crude product was purified by recrystallisation from methanol and diethyl ether, to afford 4-[(3-(2*S*)-1-[(5-bromo-1*H*-benzo[d]imidazol-2-yl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)methoxy]benzylamine as a white solid.

^{1}H-NMR (d4-CH_3OH) δ : 7.75 (1H, m), 7.50 (1H, m), 7.40-7.30 (3H, m), 6.95 (2H, m), 5.50 (1H, m), 4.80 (2H, s), 4.10 (1H, m), 3.95 (2H, m), 3.35 (1H, m), 2.05 (1H, m), 1.95 (1H, m), 1.60 (1H, m), 1.40 (3H, m).

Analysis : Found C, 47.83; H, 3.98; N, 14.97; $C_{22}H_{23}N_6O_4SBr$ requires C, 48.27; H, 4.23; N, 15.35%.

Example 57

tert-Butyl 4-[2-(3-(1*S*)-2-[(cyclohexylmethyl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)ethyl]-1-piperazinecarboxylate



The title compound was prepared by a similar method to Example 16 from *tert*-butyl 4-(3-[((*Z*)-amino(1*S*)-2-[(cyclohexylmethyl)sulfonyl]-2-piperidylmethylidene)amino]oxy-3-oxopropyl)-1-piperazinecarboxylate [see Preparation 91] and pyridine. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 90:10 changing

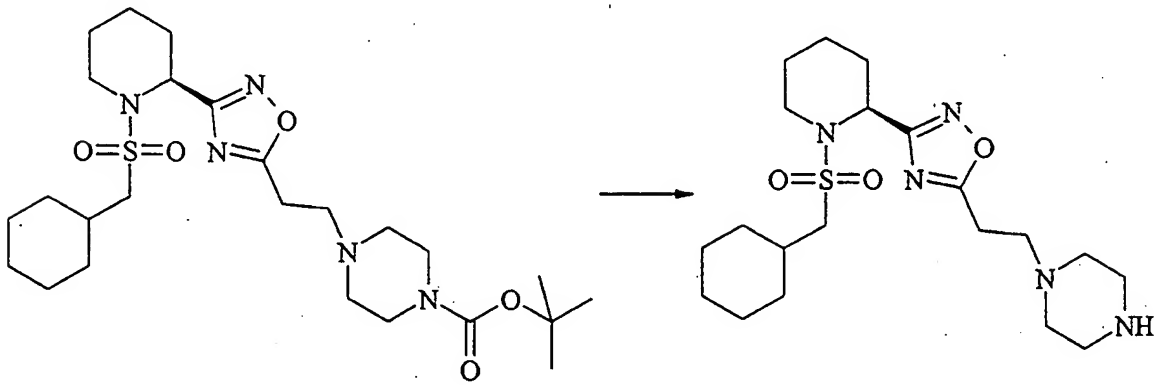
to 50:50, by volume, hexane : ethyl acetate, to afford *tert*-butyl 4-[2-(3-(1*S*)-2-[(cyclohexylmethyl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)ethyl]-1-piperazinecarboxylate as a gum.

^{1}H-NMR ($CDCl_3$) δ : 5.30 (1H, d), 3.80 (1H, d), 3.40 (4H, m), 3.20 (1H, m), 3.10 (2H, m), 3.00-2.80 (4H, m), 2.45 (4H, m), 2.25 (1H, d), 2.00 (4H, m), 1.80-1.60 (6H, m), 1.50 (9H, s), 1.40-1.00 (6H, m).

MS = 527.7 (MH^+).

Example 58

1-[2-(3-(1*S*)-2-[(Cyclohexylmethyl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)ethyl]piperazine



Trifluoroacetic acid (10ml) was added to a solution of *tert*-butyl 4-[2-(3-(1*S*)-2-[(cyclohexylmethyl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)ethyl]-1-piperazinecarboxylate (265mg) [see Example 57] in dichloromethane (10ml). The reaction mixture was stirred at room temperature for 3hrs, after which time the solvent was removed under reduced pressure and the residue partitioned

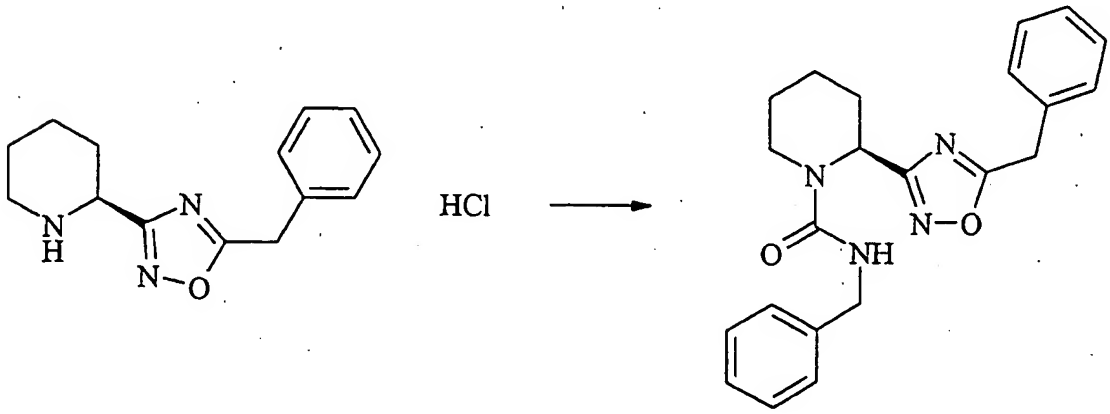
between ethyl acetate and saturated sodium hydrogen carbonate. The organic layer was separated and washed with brine, dried over magnesium sulphate and the solvent removed under reduced pressure to afford 1-[2-(3-(1*S*)-2-[(cyclohexylmethyl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)ethyl]piperazine (136mg) as a brown oil.

^{1}H-NMR ($CDCl_3$) δ : 5.30 (1H, d), 3.80 (1H, d), 3.25 (1H, t), 3.10 (2H, m), 3.00-2.80 (8H, m), 2.55 (4H, s), 2.25 (1H, d), 2.00 (5H, m), 1.80-1.60 (5H, m), 1.50 (1H, m), 1.40-1.00 (5H, m).

Analysis : Found C, 53.50; H, 8.08; N, 14.97; $C_{20}H_{35}N_5O_3S$ .1.5H_2O requires C, 53.07; H, 8.46; N, 15.47%.

Example 59

(2*S*)-*N*'-Benzyl-2-(5-benzyl-1,2,4-oxadiazol-3-yl)-1-piperidinecarboxamide



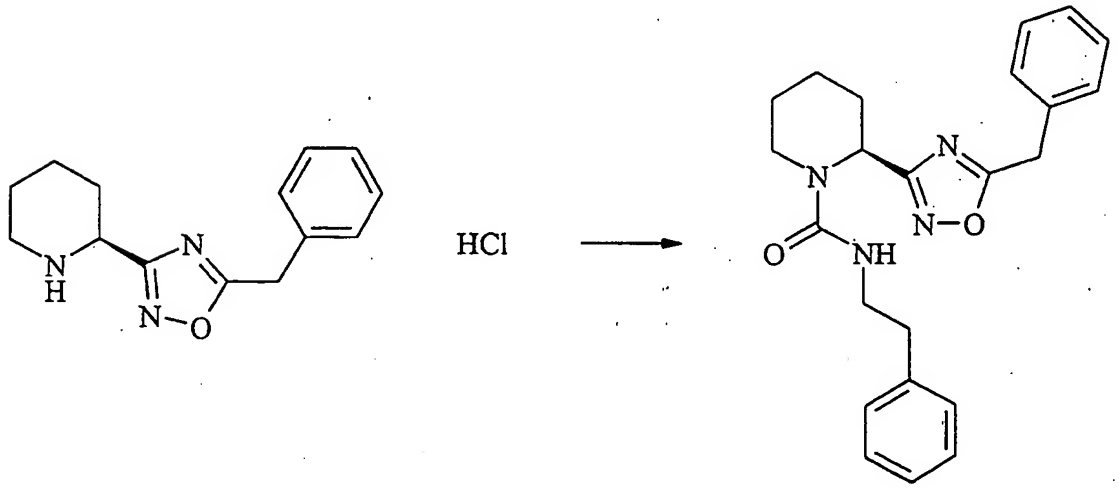
Benzyl isocyanate (68ml) was added to a suspension of 5-benzyl-3-[(2*S*)-2-piperidyl]-1,2,4-oxadiazole hydrochloride (279.8mg) [see Preparation 7] (140mg) and triethylamine (70ml) in dichloromethane (5ml). The reaction mixture was stirred for 2hrs, the crude product was then purified by column chromatography on silica gel eluting with a solvent gradient of 100:0 changing to 50:50, by volume, hexane : ethyl acetate, to afford a solid which was triturated with diethylether to afford (2*S*)-*N*'-benzyl-2-(5-benzyl-1,2,4-oxadiazol-3-yl)-1-piperidinecarboxamide (150mg) as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 7.25 (10H, m), 5.60 (1H, d), 4.95 (1H, bs), 4.40 (2H, s), 4.20 (2H, s), 3.70 (1H, d), 3.10 (1H, t), 2.25 (1H, d), 1.85 (1H, t), 1.65 (2H, m), 1.45 (2H, m).

Analysis : Found C, 70.02; H, 6.44; N, 14.87; $C_{22}H_{24}N_4O_2$ requires C, 70.19; H, 6.43; N, 14.88%.

Example 60

(2*S*)-2-(5-Benzyl-1,2,4-oxadiazol-3-yl)-*N*^{1}-phenethyl-1-piperidinecarboxamide



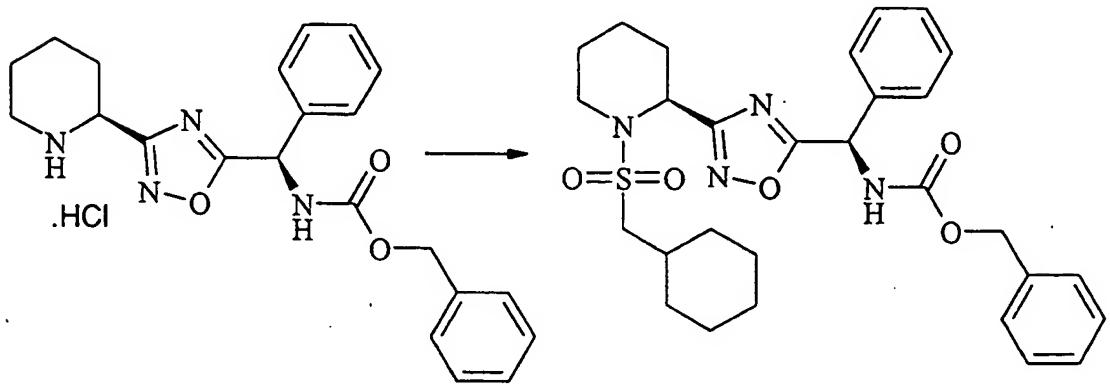
The title compound was prepared and purified by a similar method to Example 59 from 5-benzyl-3-[(2*S*)-2-piperidyl]-1,2,4-oxadiazole hydrochloride [see Preparation 7] and phenethyl isocyanate to afford (2*S*)-2-(5-benzyl-1,2,4-oxadiazol-3-yl)-*N*^{1}-phenethyl-1-piperidinecarboxamide as a gum.

^{1}H-NMR ($CDCl_3$) δ : 7.35-7.15 (10H, m), 5.55 (1H, d), 4.65 (1H, bs), 4.20 (2H, s), 3.45 (3H, m), 3.10 (1H, t), 2.80 (2H, m), 2.20 (1H, d), 1.85 (1H, m), 1.65 (2H, m), 1.50-1.35 (2H, m).

Analysis : Found C, 70.43; H, 6.77; N, 14.22; $C_{23}H_{26}N_4O_2$ requires C, 70.75; H, 6.71; N, 14.35%.

Example 61

Benzyl N-[(*R*)-(3-{(2*S*)-1-(cyclohexylmethyl)sulfonyl-2-piperidyl}-1,2,4-oxadiazol-5-yl)(phenyl)methyl]carbamate



The title compound was prepared and purified by a similar method to Example 1 from benzyl N-[(*R*)-phenyl{3-[(2*S*)-2-piperidyl]-1,2,4-oxadiazol-5-yl}methyl]carbamate hydrochloride [see Preparation 103] and cyclohexylmethylsulphonyl chloride to afford benzyl N-[(*R*)-(3-{(2*S*)-1-(cyclohexylmethyl)sulfonyl-2-piperidyl}-1,2,4-oxadiazol-5-yl)(phenyl)methyl]carbamate as a gum.

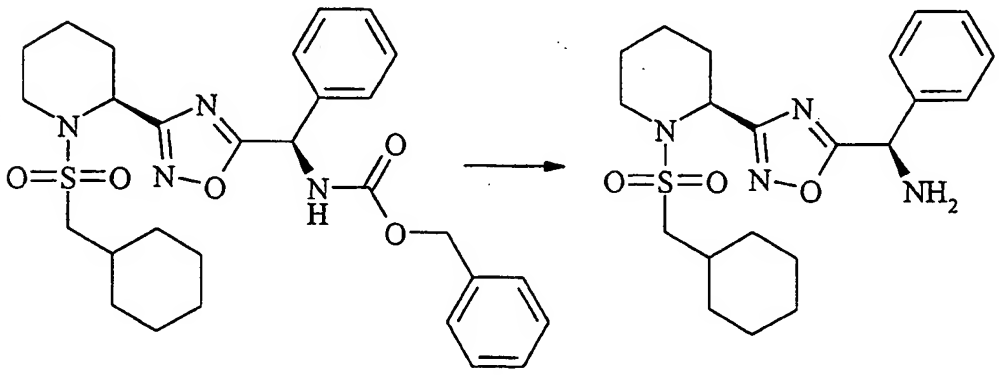
^{1}H-NMR ($CDCl_3$) δ : 7.35 (10H, m), 6.20 (1H, d), 5.75 (1H, d), 5.30 (1H, m), 5.05 (2H, m), 3.75 (1H, d), 3.20 (1H, m), 2.80 (2H, m), 2.10 (1H, d), 1.90 (4H, m), 1.60 (6H, m), 1.40 (1H, m), 1.10 (2H, m), 1.05 (1H,m), 0.95 (2H,m).

Analysis : Found C, 62.66; H, 6.55; N, 9.91; $C_{29}H_{36}N_4SO_5$. 0.2 H_2O requires C, 62.61; H, 6.60; N, 10.07%.

Rotation : $[\alpha]_D^{25}$ = -30° (c = 0.1, methanol).

Example 62

(*R*)-(3-{(2*S*)-1-[(Cyclohexylmethyl)sulfonyl]-2-piperidyl}-1,2,4-oxadiazol-5-yl)(phenyl)methylamine



The title compound was prepared and purified by a similar method to Example 27 from benzyl N-[(*R*)-(3-{(2*S*)-1-(cyclohexylmethyl)sulfonyl-2-piperidyl}-1,2,4-oxadiazol-5-yl)(phenyl)methyl]carbamate [see Example 61] and 45% w/w hydrogen bromide in glacial acetic acid to afford (*R*)-(3-{(2*S*)-1-[(cyclohexylmethyl)sulfonyl]-2-piperidyl}-1,2,4-oxadiazol-5-yl)(phenyl)methylamine as a gum.

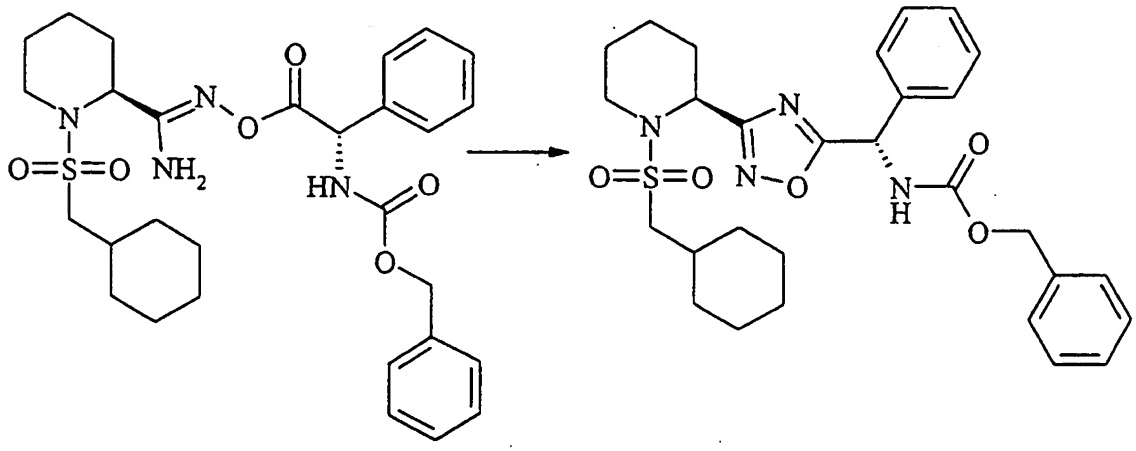
^{1}H-NMR ($CDCl_3$) δ : 7.40 (5H, m), 5.40 (1H, s), 5.30 (1H, m), 3.75 (1H, d), 3.20 (1H, m), 2.85 (2H, m), 2.30 (1H, m), 1.95 (6H, m), 1.65 (6H, m), 1.50 (1H, m), 1.20 (3H, m), 0.95 (2H,m).

Analysis : Found C, 59.97; H, 7.21; N, 13.00; $C_{21}H_{30}N_4SO_3$. requires C, 60.26; H, 7.22; N, 13.39%.

Rotation : $[\alpha]_D^{25}$ = -49° (c = 0.1, methanol).

Example 63

Benzyl N-[(*S*)-(3-{(2*S*)-1-(cyclohexylmethyl)sulfonyl-2-piperidyl}-1,2,4-oxadiazol-5-yl)(phenyl)methyl]carbamate



The title compound was prepared and purified by a similar method to Example 16 from benzyl-N-[(1*S*)-2-{[((*Z*)-amino{(2*S*)-1-[(cyclohexylmethyl)sulfonyl]-2-piperidyl}methylidene)amino]oxy}-2-oxo-1-phenylethyl]carbamate [see Preparation 104] and toluene to afford benzyl N-[(*S*)-(3-{(2*S*)-1-(cyclohexylmethyl)sulfonyl-2-piperidyl}-1,2,4-oxadiazol-5-yl)(phenyl)methyl]carbamate as a gum.

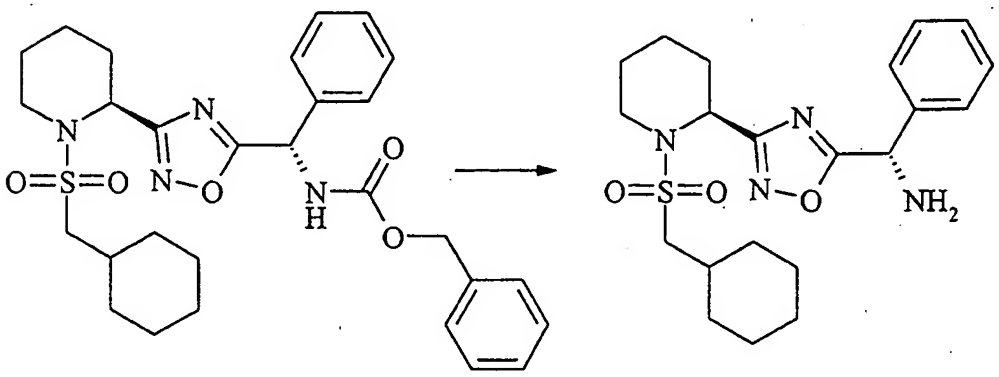
^{1}H-NMR ($CDCl_3$) δ : 7.40 (10H, m), 6.20 (1H, d), 5.70 (1H, s), 5.30 (1H, m), 5.15 (2H, m), 3.75 (1H, d), 3.20 (1H, m), 2.80 (2H, m), 2.15 (1H, m), 1.90 (4H, m), 1.60 (6H, m), 1.40 (1H, m), 1.20 (3H, m), 0.95 (2H,m).

Analysis : Found C, 62.92; H, 6.59; N, 10.05; $C_{29}H_{36}N_4SO_5$. requires C, 63.02; H, 6.57; N, 10.14%.

Rotation : $[\alpha]_D^{25}$ = -20° (c = 0.1, methanol).

Example 64

(*S*)-(3-{(2*S*)-1-[(Cyclohexylmethyl)sulfonyl]-2-piperidyl}-1,2,4-oxadiazol-5-yl)(phenyl)methylamine



The title compound was prepared and purified by a similar method to Example 27 from benzyl N-[(*S*)-(3-{(2*S*)-1-(cyclohexylmethyl)sulfonyl-2-piperidyl}-1,2,4-oxadiazol-5-yl)(phenyl)methyl]carbamate [see Example 63] to afford (*S*)-(3-{(2*S*)-1-[(cyclohexylmethyl)sulfonyl]-2-piperidyl}-1,2,4-oxadiazol-5-yl)(phenyl)methylamine as a gum.

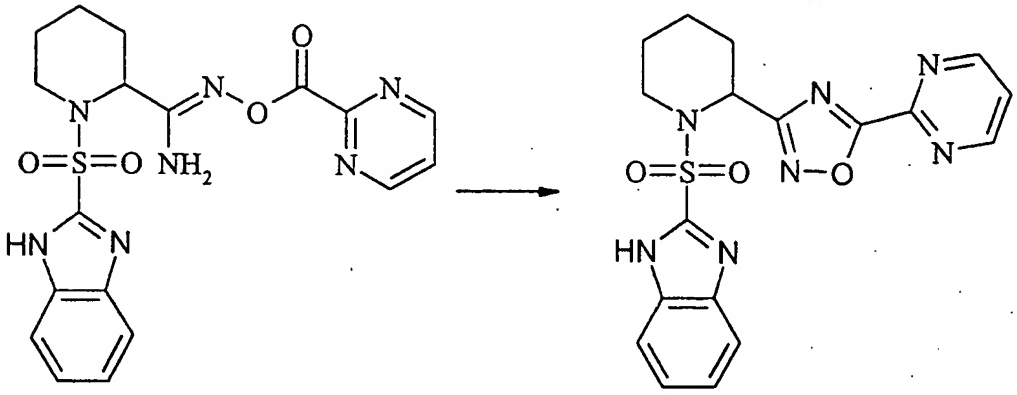
^{1}H-NMR ($CDCl_3$) δ : 7.30 (5H, m), 5.40 (1H, s), 5.30 (1H, d), 3.75 (1H, d), 3.20 (1H, m), 2.85 (2H, m), 2.25 (1H, m), 2.10 (2H, m), 1.90 (4H, m), 1.60 (6H, m), 1.45 (1H, m), 1.20 (3H, m), 0.95 (2H,m).

Analysis : Found C, 60.07; H, 7.21; N, 13.04; $C_{21}H_{30}N_4SO_3$. requires C, 60.26; H, 7.22; N, 13.39%.

Rotation : $[\alpha]_D^{25}$ = -46.2° (c = 0.1, methanol).

Example 65

2-({2-[5-(2-pyrimidinyl)-1,2,4-oxadiazol-3-yl]-2-piperidyl}sulfonyl)-1*H*-benzo[d]imidazole



The title compound was prepared by the method of Preparation 13 from 1-(1*H*-benzo[d]imidazol-2-ylsulfonyl)-N'²-[(2-pyrimidinylcarbonyl)oxy]-2-piperidinecarboximidamide [see Preparation 105] and pyridine, to afford 2-({(2-[5-(2-pyrimidinyl)-1,2,4-oxadiazol-3-yl]-2-piperidyl}sulfonyl)-1*H*-benzo[d]imidazole as a solid.

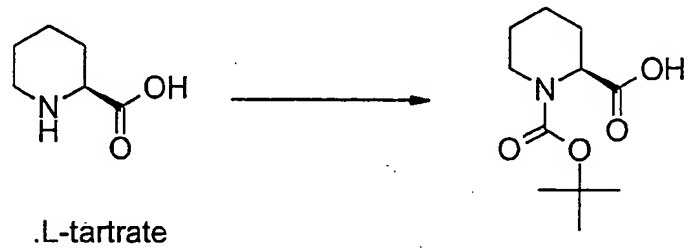
^{1}H-NMR ($CDCl_3$) δ : 9.10 (2H, s), 7.85 (1H, d), 7.65 (2H, m), 7.35 (2H, m), 5.80 (1H, s), 3.90 (1H, d), 3.00 (1H, t), 2.55 (1H, d), 2.15 (1H, m), 1.90-1.60 (4H, m). Analysis : Found C, 52.12; H, 4.13; N, 23.09; $C_{18}H_{17}N_7SO_3$. 0.1 CH_2Cl_2 requires C, 51.77; H, 4.13; N, 23.35%.

It should be noted that Preparations 21, 23, 42, 79, 86 and 96 in the following Preparations section also illustrate the syntheses of compounds of the formula (I).

The following Preparations describe the preparation of certain intermediates used in the preceding Examples.

Preparation 1

(2*S*)-1-(*tert*-Butoxycarbonyl)-2-piperidinecarboxylic acid

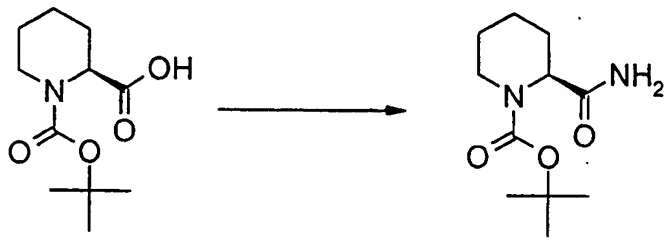


.L-tartrate

(2S)-2-Piperidinecarboxylic acid L-tartrate (55.0g) (see WO-A-96/11185) was dissolved in water (200ml). The resulting solution was cooled to 0°C and di-t-butyldicarbonate (86g) in 1,4-dioxane (203ml) was added followed by 1N aqueous sodium hydroxide solution (610ml) over a period of 20 mins.. The reaction mixture was stirred at 0°C for 1 hour and then at room temperature for 56 hours. The solvent was then removed under reduced pressure and the resulting solid was dissolved in water (100ml) and washed with diethyl ether (1000ml). The aqueous layer was acidified to pH 2.0 with 1M aqueous citric acid solution (500ml) and the product was extracted with ethyl acetate (4x500ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure to afford (2*S*)-1-(*tert* butoxycarbonyl)-2-piperidinecarboxylic acid (19.55g) as a white solid. ^{1}H-NMR (d_6-DMSO) δ: 12.7 (1H, bs), 4.55 (1H, d), 3.80 (1H, s), 2.90-2.60 (1H, m), 2.05 (1H, m), 1.60 (3H, m), 1.30 (10H, d), 1.10 (1H, m).

Preparation 2

tert-Butyl (2*S*)-2-(aminocarbonyl)-1-pip ridinecarboxylate

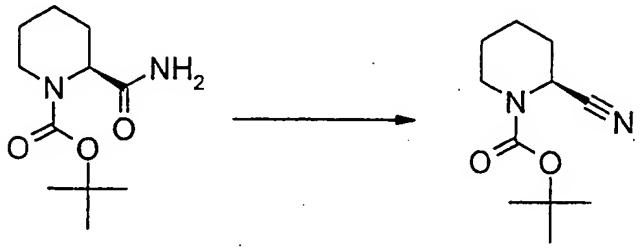


Triethylamine (14.46ml) was added to a solution of (2*S*)-1-(*tert*-butoxycarbonyl)-2-piperidinecarboxylic acid (18.3g) [see Preparation 1] in tetrahydrofuran (240ml) at -20°C under an atmosphere of nitrogen. Ethyl chloroformate (7.52ml) was then added to the mixture and the resulting solution was stirred for 40 mins. at -10°C and then 0.88 aqueous ammonia solution (32ml) added. The reaction mixture was stirred for 10 mins. after which time the solvent was removed under reduced pressure and the residue diluted with ethyl acetate and water. The organic layer was separated and dried over magnesium sulphate and the solvent was removed under reduced pressure to afford *tert*-butyl (2*S*)-2-(aminocarbonyl)-1-piperidinecarboxylate (18.65g) as a white solid.

^{1}H-NMR ($CDCl_3$) δ: 6.0 (1H, bs), 5.40 (1H, bs), 4.80 (1H, s). 4.00 (1H, m), 2.85 (1H, t), 2.30 (1H, d), 1.80-1.40 (14H, m).

Preparation 3

tert-Butyl (2*S*)-2-cyano-1-piperidinecarboxylate



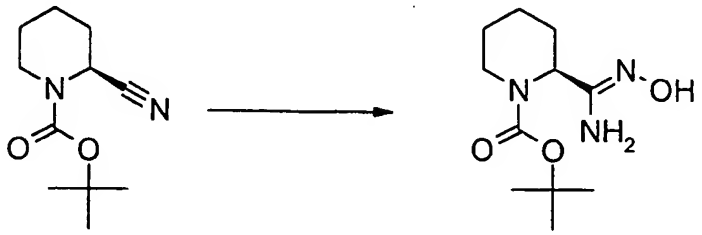
Oxalyl chloride (8.54ml) was added to a stirred solution of dimethylformamide (7.57ml) in acetonitrile (440ml) at -5°C under an atmosphere of nitrogen. The mixture was stirred for 15 mins., after which time a solution of *tert*-butyl (2*S*)-2-(aminocarbonyl)-1-piperidinecarboxylate (18.63g) [see Preparation 2] and pyridine (16.50ml) in acetonitrile (100ml) was added and the resulting solution was stirred for 10 mins.. The mixture was then reduced to low volume under reduced presssure and diluted with ethyl acetate (1000ml) and water (1000ml). The organic layer was separated, dried over magnesium sulphate and the solvent removed under reduced pressure to afford *tert*-butyl (2*S*)-2-cyano-1-piperidinecarboxylate (13.7g) as a white solid.

^{1}H-NMR ($CDCl_3$) δ: 5.20 (1H, s), 4.00 (1H, m), 2.90 (1H, t), 1.90 (1H, d), 1.80-1.60 (4H, m), 1.40 (9H, s), 1.40 (1H, m).

Rotation : $[\alpha]_D^{25}$ = -136.83° (c = 0.1, methanol).

Preparation 4

tert-Butyl (Z)-(2*S*)-2-[amino(hydroxyimino)methyl]-1-piperidinecarboxylate

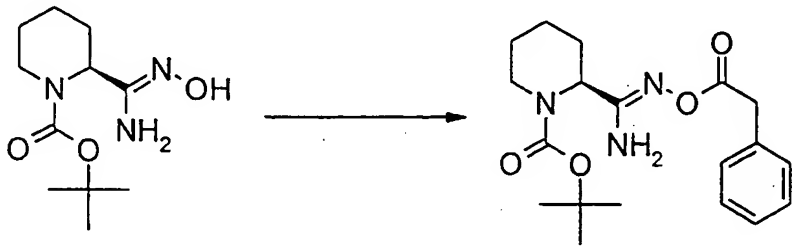


A solution of *tert*-butyl (2*S*)-2-cyano-1-piperidinecarboxylate (13.10g) [see Preparation 3] in methanol (500ml) was added to a solution of hydroxylamine hydrochloride (21.6g) and sodium carbonate (33.0g) in water (600ml). The reaction mixture was warmed to the reflux temperature and stirred for 8 hours after which time the methanol was removed under reduced pressure and the product extracted from the aqueous layer with ethyl acetate (3x500ml). The combined organic layers were washed with water (500ml), dried over magnesium sulphate and the solvent removed under reduced pressure to afford *tert*-butyl (Z)-(2*S*)-2-[amino(hydroxyimino)methyl]-1-piperidinecarboxylate (14.1g) as a white solid.

^{1}H-NMR ($CDCl_3$) δ: 7.10 (1H, bs), 4.95 (1H, s), 4.70 (2H, bs), 4.00 (1H, d), 2.90 (1H, t), 2.15 (1H, d), 1.80 (1H, t), 1.60-1.30 (13H, m).
MS : 244 (MH^+).

Preparation 5

tert-Butyl (Z)-(2*S*)-2-(amino[(2-phenylacetyl)oxy]iminomethyl)-1-piperidinecarboxylate



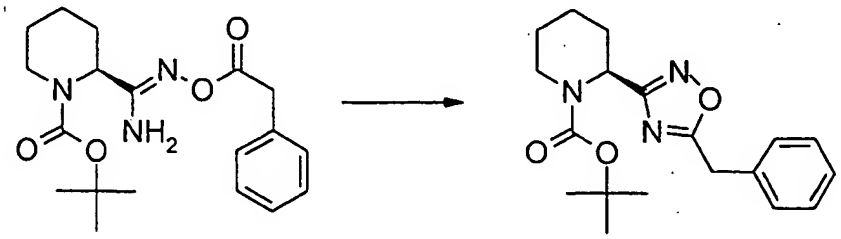
1-Hydroxybenzotriazole hydrate (8.67g), phenylacetic acid (8.0g), N-methylmorpholine (14.69ml), 4-dimethylaminopyridine (3.3g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (12.29g) were added to a solution of *tert*-butyl (Z)-(2*S*)-2-[amino(hydroxyimino)methyl]-1-piperidinecarboxylate (13.0g) [see Preparation 4] in dichloromethane (180ml). The reaction mixture was stirred for 2 hours under an atmosphere of nitrogen, after which time the mixture was diluted with dichloromethane and 1N aqueous citric acid solution. The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate solution, dried over magnesium sulphate and the solvent was removed under reduced pressure to afford *tert*-butyl (Z)-(2*S*)-2-(amino[(2-phenylacetyl)oxy]iminomethyl)-1-piperidinecarboxylate (17.63g) as a white solid.

^{1}H-NMR ($CDCl_3$) δ: 7.30 (5H, m), 4.90 (1H, s), 4.80 (2H, bs), 4.00 (1H, d), 3.75 (2H, s), 2.75 (1H, t), 2.20 (1H, d), 1.80 (1H, m), 1.60-1.30 (13H, m).

Rotation : $[\alpha]_D^{25}$ = -64.0° (c = 0.1, methanol).

Preparation 6

tert-Butyl (2*S*)-2-(5-benzyl-1,2,4-oxadiazol-3-yl)-1-piperidinecarboxylate

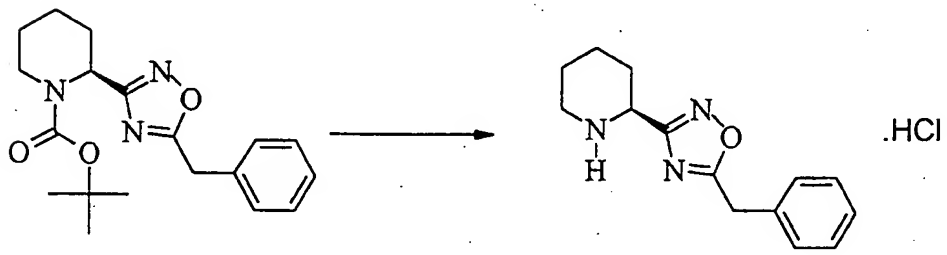


tert-Butyl (Z)-(2*S*)-2-(amino[(2-phenylacetyl)oxy]iminomethyl)-1-piperidinecarboxylate (17.5g) [see Preparation 5] was dissolved in xylene (500ml) and heated under reflux for 17 hours. The crude reaction mixture was chromatographed on silica gel eluting with a solvent gradient of 0:100 changing to 20:80, by volume, ethyl acetate : hexane to afford *tert*-butyl (2*S*)-2-(5-benzyl-1,2,4-oxadiazol-3-yl)-1-piperidinecarboxylate (10.56g) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 7.30 (5H, m), 5.40 (1H, s), 4.20 (2H, s), 4.00 (1H, d), 3.00 (1H, t), 2.20 (1H, d), 1.80 (1H, m), 1.60-1.30 (13H, m).

Preparation 7

5-Benzyl-3-[(2*S*)-2-piperidyl]-1,2,4-oxadiazole hydrochloride



tert-Butyl (2*S*)-2-(5-benzyl-1,2,4-oxadiazol-3-yl)-1-piperidinecarboxylate (10.59g) [see Preparation 6] was dissolved in dichloromethane (150ml) and cooled to 0°C. Hydrogen chloride gas was then bubbled through until the point of saturation. The reaction mixture was then stirred for 30 mins. at 0°C, the solvent was removed under reduced pressure and the product azeotroped with dichloromethane to afford 5-benzyl-3-[(2*S*)-2-piperidyl]-1,2,4-oxadiazole hydrochloride (8.3g) as a yellow solid.

^{1}H-NMR ($CDCl_3$): δ 10.00 (1H, bs), 7.30 (5H, m), 4.45 (1H, s), 4.20 (2H, s), 3.65 (1H, m), 3.20 (1H, m), 2.40 (1H, m), 2.10 (1H, m), 2.00 (1H, m), 1.90-1.60 (3H, m).

Rotation : $[\alpha]_D^{25}$ = -15.20° (c = 0.1, methanol).

Analysis : Found C, 59.38; H, 6.47; N, 14.76; $C_{14}H_{17}N_3O.HCl.\ 0.05\ CH_2Cl_2$ requires C, 59.42; H, 6.42; N, 14.79%

Preparation 8

1*H*-Benzo[*d*]imidazole-2-sulfonyl chloride

1*H*-2-Benzo[*d*]imidazolethiol (1.5g) was suspended in 20% v/v acetic acid/water (60ml) and cooled to 0°C. Chlorine gas was bubbled through the mixture until a point of saturation. The reaction mixture was stirred for 1hour after which time it was filtered and the resulting solid was washed with ice-cold water and dried under reduced pressure to afford 1*H*-benzo[*d*]imidazole-2-sulfonyl chloride (2.38g) as a light brown solid.

^{1}H-NMR (d_6-DMSO) δ: 7.70 (2H, d), 7.55 (2H, d).

Preparation 9

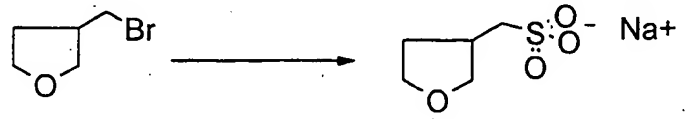
3-(Bromomethyl)tetrahydrofuran

A solution of triphenylphosphine (7.34g) in dichloromethane (65ml) was added to a solution of 3-(hydroxymethyl)tetrahydrofuran (1.93ml) and carbon tetrabromide (7.95g) in dichloromethane (55ml) at 0°C. The solution was warmed to room temperature and the reaction mixture was stirred for 3.5 hours after which time the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with a solvent gradient of 15:1 changing to 10:1, by volume, hexane : ethyl acetate to afford 3-(bromomethyl)tetrahydrofuran (2.49g) as a colourless oil.

^{1}H-NMR ($CDCl_3$) δ: 3.85 (2H, m), 3.75 (1H, q), 3.58 (1H, m), 3.40 (2H, q), 2.65 (1H, m), 2.10 (1H, m), 1.65 (1H, m).

Preparation 10

Sodium tetrahydrofuran-3-ylmethanesulfonate



Sodium sulfite heptahydrate (6.10g) was added to a solution of 3-(bromomethyl)tetrahydrofuran (2.0g) [see Preparation 9] in 1,4-dioxane (9ml) and water (9ml). The reaction mixture was then heated under reflux and stirred for 18 hours, cooled and the solvent removed under reduced pressure. The resulting solid was dissolved in water and concentrated to a low volume. The solid formed was then collected to afford sodium tetrahydrofuran-3-ylmethanesulfonate (1.30g) as a white solid.

^{1}H-NMR (D_2O) δ: 3.95 (1H, m), 3.80-3.60 (2H, m), 3.45 (1H, m), 3.00 (2H, m), 2.60 (1H, m), 2.20 (1H, m), 1.65 (1H, m).

Preparation 11

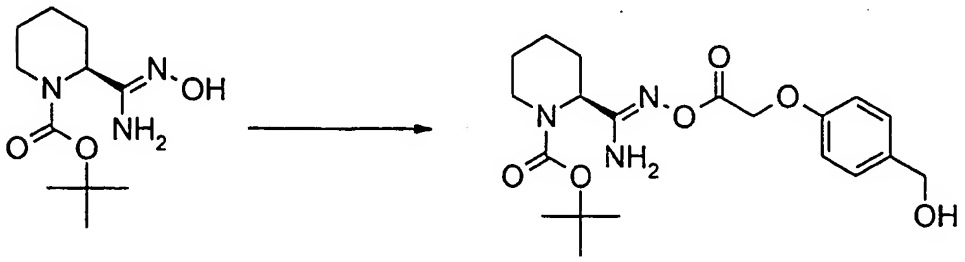
Tetrahydrofuran-3-ylmethanesulfonyl chloride

Sodium tetrahydrofuran-3-ylmethanesulfonate (1.0g) [see Preparation 10] was dissolved in dimethylformamide (0.05ml) and thionyl chloride (5.3ml) was added. The reaction mixture was heated under reflux for 5 hours, cooled and toluene (10ml) added. The solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water, the organic layer was separated, washed with brine, dried over magnesium sulphate and the solvent removed under reduced pressure to afford tetrahydrofuran-3-ylmethanesulfonyl chloride (0.22g) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ : 3.95 (1H, m), 3.90-3.60 (2H, m), 3.45 (1H, m), 3.00 (2H, m), 2.30 (1H, m), 2.10 (1H, m), 1.80 (1H, m).

Preparation 12

tert-Butyl (Z)-(2S)-2-amino[(2-[4-(hydroxymethyl)phenoxy]acetyloxy)imino]methyl-1-piperidinecarboxylate

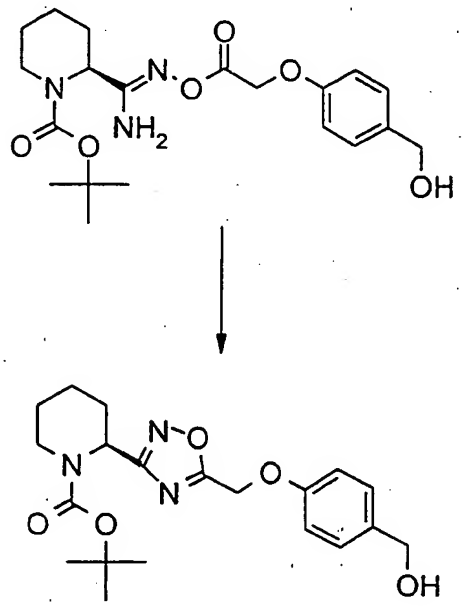


To a stirred solution of *tert*-butyl (Z)-(2*S*)-2-[amino(hydroxyimino)methyl]-1-piperidinecarboxylate [see Preparation 4] (2.43g) in dichloromethane (75ml) was added 4-(hydroxymethyl)phenoxyacetic acid (2.19g), 1-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride (2.30g), 4-dimethylaminopyridine (0.611g) and N-methylmorpholine (1.30ml). The reaction mixture was stirred for 56 hours, after which time it was diluted with dichloromethane (200ml) and washed with 1M aqueous hydrochloric acid solution (50ml) followed by saturated aqueous sodium hydrogen carbonate solution (50ml). The organic layer was separated, dried over magnesium sulphate and the solvent was removed under reduced pressure to afford *tert*-butyl (Z)-(2S)-2-amino[(2-[4-(hydroxymethyl)phenoxy]acetyloxy)imino]methyl-1-piperidinecarboxylate (2.94g).

^{1}H-NMR ($CDCl_3$) δ : 7.30 (2H, m), 7.00 (2H, m), 6.85 (1H, d), 5.55 (1H, bs), 5.30 (2H, s), 5.20 (1H, s), 4.60 (3H, m), 4.00 (1H, d), 3.00 (1H, d), 2.30 (1H, d), 1.90 (1H, m), 1.80-1.30 (13H, m).

Preparation 13

tert-Butyl (2*S*)-2-(5-[4-(hydroxymethyl)phenoxymethyl]-1,2,4-oxadiazol-3-yl)-1-piperidinecarboxylate

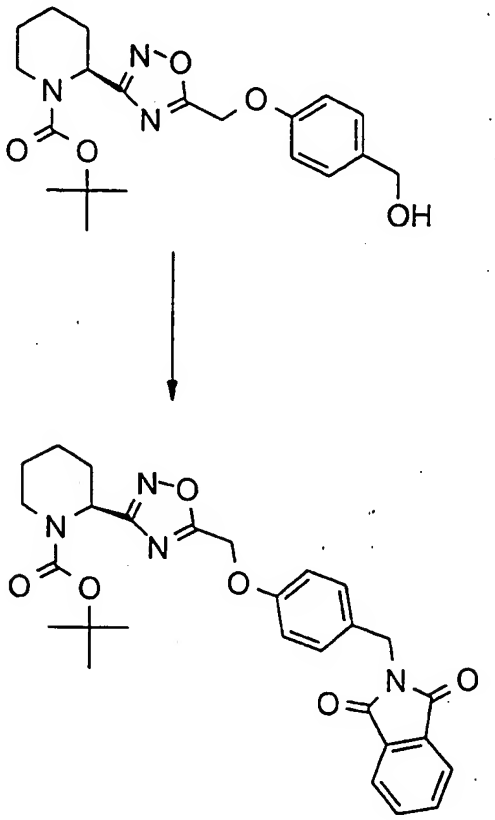


tert-Butyl (Z)-(2S)-2-amino[(2-[4-(hydroxymethyl)phenoxy]acetyloxy) imino]methyl-1-piperidinecarboxylate [see Preparation 12] (2.94g) was dissolved in pyridine (30ml) and heated under reflux for 18 hours. The reaction mixture was cooled and the solvent removed under reduced pressure. The residue was partitioned between ethyl acetate and water, the organic layer was separated , dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 50:50 changing to 0:100 (in 10% increments), by volume, hexane : ethyl acetate to afford *tert*-butyl (2*S*)-2-(5-[4-(hydroxymethyl)phenoxymethyl]-1,2,4-oxadiazol-3-yl)-1-piperidinecarboxylate (1.06g).

^{1}H-NMR ($CDCl_3$) δ : 7.30 (2H, d), 7.00 (2H, d), 5.50 (1H, bs), 5.25 (2H, s), 4.65 (2H, d), 4.00 (1H, d), 3.00 (1H, t), 2.25 (1H, d), 1.90 (1H, m), 1.75-1.40 (13H, m).

Preparation 14

***tert*-Butyl (2*S*)-2-[5-(4-[(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)methyl]phenoxymethyl)-1,2,4-oxadiazol-3-yl]-1-piperidinecarboxylate**



Phthalimide (480mg) was added to a solution of *tert*-butyl (2*S*)-2-(5-[4-(hydroxymethyl)phenoxymethyl]-1,2,4-oxadiazol-3-yl)-1-piperidinecarboxylate [see Preparation 13] (1.06g) in tetrahydrofuran (10ml). The mixture was cooled to 0°C and triphenylphosphine (1.07g) was added followed by diethylazodicarboxylate (0.642ml). The resulting yellow solution was stirred at 0°C for 10mins. and then at room temperature for 1 hour. The mixture was evaporated to a low volume under reduced pressure and partitioned between dichloromethane and water. The organic layer was separated, washed with brine, dried over magnesium sulphate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 90:10 changing to 70:30, by

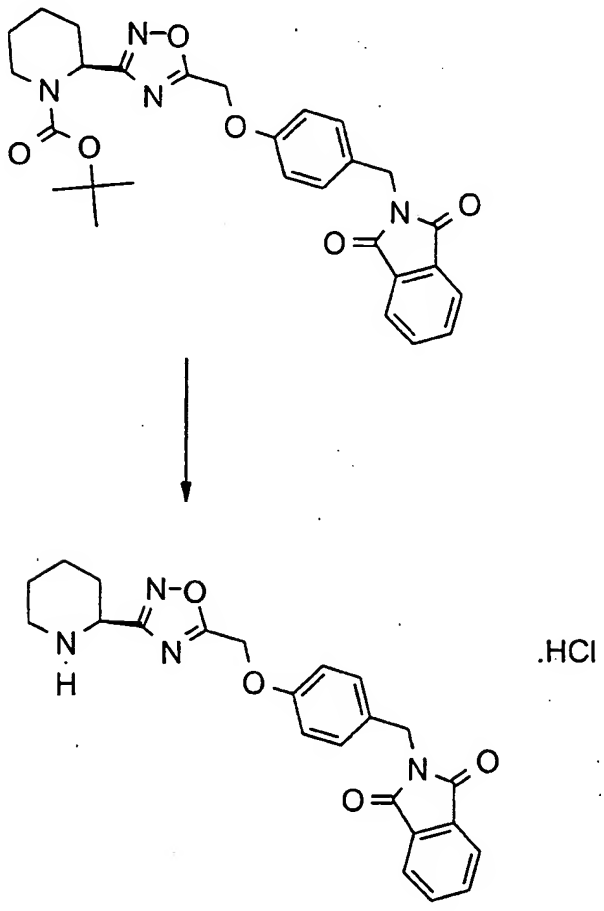
volume, hexane : ethyl acetate to afford *tert*-butyl (2*S*)-2-[5-(4-[(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)methyl]phenoxymethyl)-1,2,4-oxadiazol-3-yl]-1-piperidinecarboxylate (1.09g) as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 7.90 (2H, s), 7.70 (2H, s), 7.40 (2H, m), 6.90 (2H, m), 5.45 (1H, bs), 5.20 (2H, d), 4.80 (2H, d), 4.00 (1H, m), 3.00 (1H, bs), 2.25 (1H, m), 1.80 (1H, bs), 1.70-1.30 (13H, m).

Analysis : Found C, 63.85; H, 5.91; N, 10.03; $C_{28}H_{30}N_4O_6$. 0.5 EtOAc requires C, 64.04; H, 6.09; N, 9.96%. (EtOAc = ethyl acetate).

Preparation 15

2-[4-(3-[(2S)-2-Piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzyl]-1,3-isoindolinedione hydrochloride

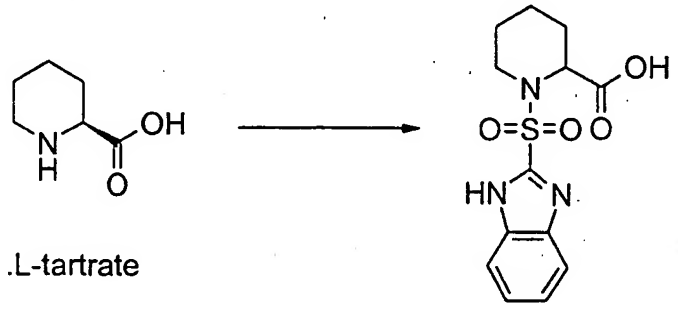


The title compound was prepared by the method of Preparation 7 from *tert*-butyl (2*S*)-2-[5-(4-[(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)methyl]-phenoxymethyl)-1,2,4-oxadiazol-3-yl]-1-piperidinecarboxylate [see Preparation 14] and hydrogen chloride gas to afford 2-[4-(3-[(2*S*)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzyl]-1,3-isoindolinedione hydrochloride as a white solid.

^{1}H-NMR (d_6-DMSO) δ : 7.85 (4H, m), 7.30 (2H, d), 7.00 (2H, d), 5.60 (2H, s), 4.70 (3H, d), 3.05 (1H, t), 2.20 (1H, d), 1.90-1.50 (6H, m).

Preparation 16

1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidinecarboxylic acid

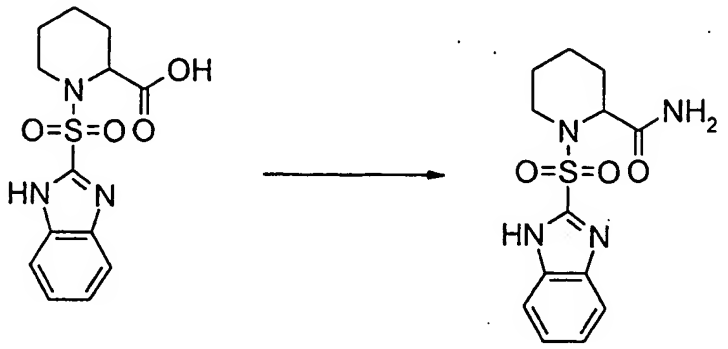


(2S)-2-Piperidinecarboxylic acid L-tartrate (42g) [see Preparation 1] was dissolved in 10% w/w aqueous sodium hydroxide solution (600ml) and 1*H*-benzo[*d*]imidazole-2-sulfonyl chloride (39g) [see Preparation 8] was added. The reaction mixture was stirred at room temperature for 56 hours after which time the product was extracted with ethyl acetate. The organic layer was separated, 2N aqueous hydrochloric acid solution added and the acidic aqueous layer extracted twice with ethyl acetate. The combined organic layers were dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with 95:5:0.5, by volume, dichloromethane : methanol : glacial acetic acid to afford 1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidinecarboxylic acid (17.5g).

^{1}H-NMR (d_6-DMSO) δ : 7.25 (2H, m), 7.10 (2H, m), 4.65 (1H, s), 3.85 (1H, d), 3.20 (1H, t), 2.30 (1H, d), 1.50 (3H, m), 1.20 (2H, m).

Preparation 17

1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidinecarboxamide

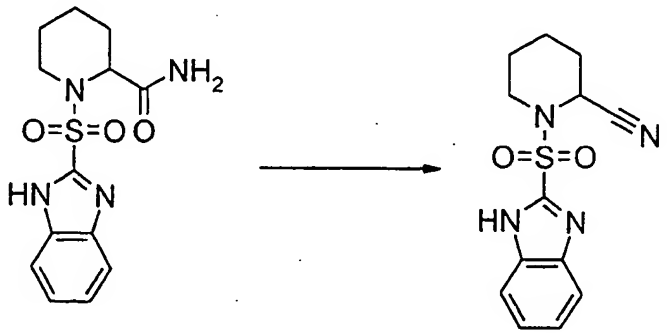


1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidinecarboxylic acid (17.5g) [see Preparation 16] was dissolved in tetrahydrofuran (180ml) and cooled to -20°C. Triethylamine (10.2ml) was added to the mixture followed by ethyl chloroformate (5.4ml). The reaction mixture was stirred for 1 hour at -20°C and 0.88 aqueous ammonia solution (25ml) was added. The mixture was then stirred for a further 2 hours at room temperature. The organic solvent was removed under reduced pressure and ethyl acetate added. The organic layer was separated, washed with water, dried over magnesium sulphate and the solvent removed under reduced pressure to afford 1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidinecarboxamide (14.73g).

^{1}H-NMR ($CDCl_3$) δ : 8.80 (1H, s), 7.70 (2H, m), 7.40 (2H, m), 6.00 (1H, bs), 5.00 (1H, s), 3.80 (1H, d), 3.20 (1H, t), 2.60 (1H, d), 1.80-1.50 (5H, m).

Preparation 18

1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidinecarbonitrile

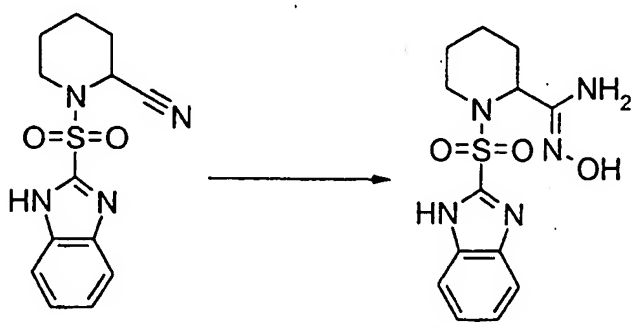


Oxalyl chloride (5.00ml) was added dropwise to a solution of dimethylformamide (4.43ml) in acetonitrile (200ml) at 0°C. The mixture was stirred for 20 mins. and a suspension of pyridine (9.66ml) and 1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidinecarboxamide (14.73g) [see Preparation 17] in acetonitrile (100ml) was added over a period of 10 mins.. The reaction mixture was stirred for a further 20 mins. after which time the solvent was removed under reduced pressure. The residue was diluted with diethyl ether and washed with water, brine, dried over magnesium sulphate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with 70:30, by volume, hexane : ethyl acetate to afford 1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidinecarbonitrile (4.9g).

^{1}H-NMR ($CDCl_3$) δ : 7.80 (1H, m), 7.60 (1H, m), 7.30 (2H, m), 5.20 (1H, s), 4.00 (1H, d), 3.00 (1H, t), 2.00 (1H, m), 1.80 (2H, m), 1.40 (3H, m).

Preparation 19

(Z)-1-(1H-B nzo[d]imidazol-2-ylsulfonyl)-N'²-hydroxy-2-piperidinecarboximidamide

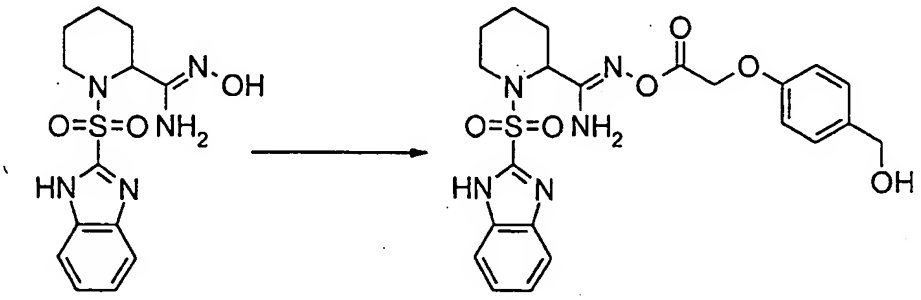


The title compound was prepared by a similar method to Preparation 4 from 1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidinecarbonitrile [see Preparation 18] to afford the title compound as an oil.

^{1}H-NMR (d_6-DMSO) δ : 9.40 (1H, bs), 7.70 (2H, s), 7.40 (2H, m), 5.60 (2H, bs), 4.80 (1H, s), 3.80 (1H, d), 3.20 (1H, t), 2.00 (1H, d), 1.60-1.30 (5H, m).

Preparation 20

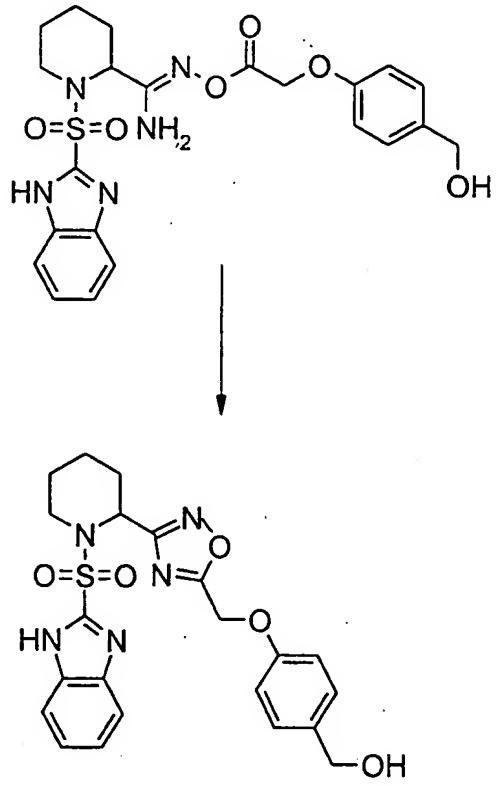
(Z)-1-(1H-Benzo[d]imidazol-2-ylsulfonyl)-N'²-(2-[4-(hydroxymethyl)phenoxy]acetyloxy)-2-piperidinecarboximidamide



The title compound was prepared by a similar method to Preparation 12 from the compound of Preparation 19 and 4-(hydroxymethyl)phenoxyacetic acid. The crude title compound was used without purification in Preparation 21.

Preparation 21

4-(3-[1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)phenylmethanol

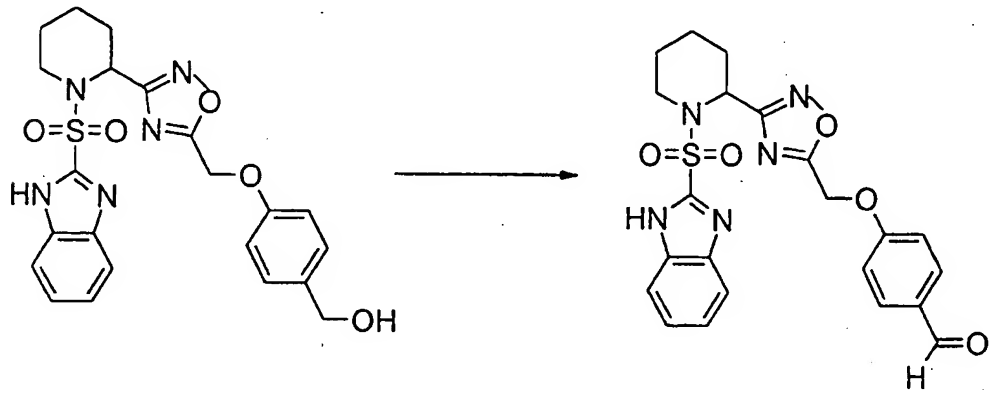


The title compound was prepared by a similar method to Preparation 13 from the compound of Preparation 20 and pyridine to afford 4-(3-[1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)phenylmethanol as an oil.

^{1}H-NMR ($CDCl_3$) δ : 7.80 (1H, m), 7.50 (1H, m), 7.30 (4H, m), 6.80 (2H, m), 5.60 (1H, d), 4.80 (2H, d), 4.60 (2H, s), 4.00 (1H, d), 3.20 (1H, m), 2.30 (1H, d), 2.10 (1H, m), 1.80 (4H, m).

Preparation 22

4-(3-[1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzaldehyde

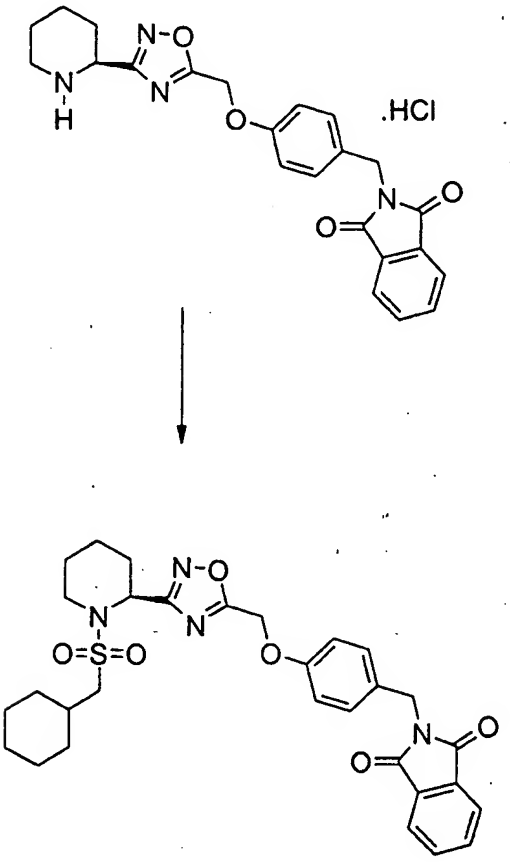


Tetrapropylammonium perruthenate (14.4mg) was added to a stirred suspension of 4-(3-[1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)phenylmethanol (384mg) [see Preparation 21], N-methylmorpholine oxide (166mg) and 4A° molecular sieves in 10% v/v acetonitrile/dichloromethane (4ml). The reaction mixture was stirred for 1 hour after which time the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with ethyl acetate to afford 4-(3-[1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzaldehyde (342mg).

^{1}H-NMR ($CDCl_3$) δ : 10.40 (1H, bs), 9.95 (1H, s), 7.85 (2H, d), 7.50-7.20 (4H, m), 7.00 (2H, d), 5.50 (1H, d), 4.80 (2H, q), 4.05 (1H, d), 3.25 (1H, t), 2.25 (1H, m), 2.10 (1H, m), 1.80 (4H, m).

Preparation 23

2-[4-(3-[(2S)-1-Cyclohexylmethylsulfonyl-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzyl]-1,3-isoindolinedione



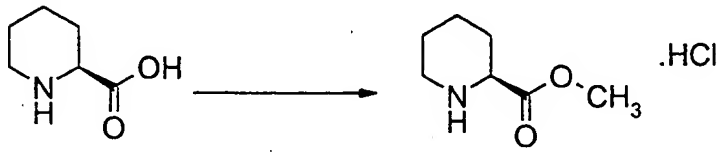
Cyclohexylmethanesulfonyl chloride (359mg) [King. J.F. et al., J.Am.Chem.Soc., 1992, 114(5), 1743-9] was added to a solution of 2-[4-(3-[(2*S*)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzyl]-1,3-isoindolinedione hydrochloride (627mg) [see Preparation 15] and triethylamine (0.4ml) in dichloromethane (2ml). The reaction mixture was stirred at room temperature for 18 hours after which time it was heated to 30°C and stirred for a further 56 hours. The mixture was diluted with dichloromethane and washed with dilute aqueous hydrochloric acid solution, the organic layer dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with a solvent

gradient of 100:0 changing to 75:25, by volume, hexane : ethyl acetate to afford 2-[4-(3-[(2S)-1-cyclohexylmethylsulfonyl-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzyl]-1,3-isoindolinedione (192mg).

^{1}H-NMR ($CDCl_3$) δ : 7.85 (2H, d), 7.70 (2H, d), 7.40 (2H, d), 6.95 (2H, d), 5.40 (1H, d), 5.20 (2H, s), 4.80 (2H, s), 3.80 (1H, d), 3.20 (1H, t), 2.90 (2H, m), 2.20 (1H, d), 2.00-1.00 (16H, m).

Preparation 24

(2*S*)-2-(Methoxycarbonyl)piperidine hydrochloride



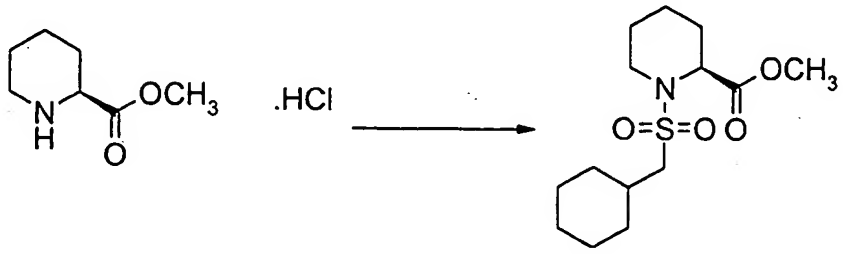
.L-tartrate

Thionyl chloride (161ml) was added dropwise to a suspension of (2S)-2-piperidinecarboxylic acid L-tartrate (60g) [see Preparation 1] in methanol (800ml) at 0°C . The reaction mixture was stirred for 18 hours at room temperature after which time the solvent was removed under reduced pressure and the product azeotroped with toluene, precipitated out using methanol and filtered to afford (2*S*)-2-(methoxycarbonyl)piperidine hydrochloride (37.7g) as a white solid.

^{1}H-NMR (D_2O) δ : 3.95 (1H, d), 3.70 (3H, s), 3.40 (1H, d), 3.00 (1H, t), 2.20 (1H, d), 1.80 (2H, d), 1.70-1.40 (3H, m).

Preparation 25

Methyl (2*S*)-1-[(cyclohexylmethyl)sulfonyl]-2-piperidinecarboxylate

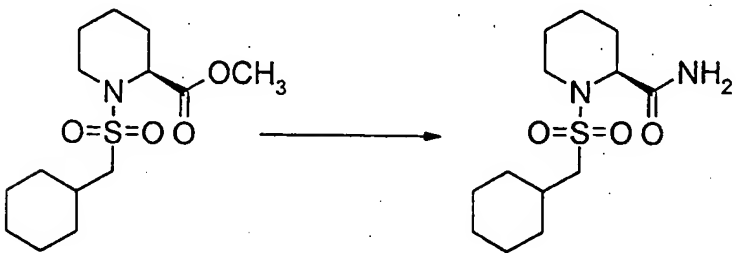


Triethylamine (22.15ml) was added to a solution of (2*S*)-2-(methoxycarbonyl)piperidine hydrochloride (10g) [see Preparation 24] and cyclohexylmethanesulfonyl chloride (16.42g) [King. J.F. et al,. J.Am.Chem.Soc., 1992, 114(5), 1743-9] in dichloromethane (100ml). The reaction mixture was stirred for 18 hours after which time the solvent was removed under reduced pressure and the residue diluted with ethyl acetate. The organic layer was washed with water, brine, dried over magnesium sulphate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 95:5 changing to 80:20, by volume, hexane : ethyl acetate to afford methyl (2*S*)-1-[(cyclohexylmethyl)sulfonyl]-2-piperidinecarboxylate (11.9g) as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 4.70 (1H, d), 3.75 (3H, s), 3.70 (1H, d), 3.20 (1H, t), 2.80 (2H, d), 2.20 (1H, d), 2.00-1.00 (16H, m).

Preparation 26

(2*S*)-1-[(Cyclohexylmethyl)sulfonyl]-2-piperidinecarboxamide



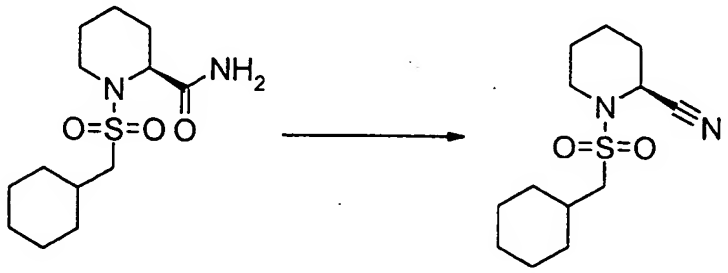
Methyl (2*S*)-1-[(cyclohexylmethyl)sulfonyl]-2-piperidinecarboxylate (3.0g) [see Preparation 25] was dissolved in 1,4-dioxane (30ml) and 0.88 aqueous ammonia solution (25ml) was added. Ammonia gas was bubbled through the mixture for 20 mins. and the reaction mixture was heated to 100°C in a sealed vessel for 56 hours. After this time the mixture was cooled and the solvent removed under reduced pressure. The residue was taken up in ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate solution, brine, dried over magnesium sulphate and the solvent was removed under reduced pressure to afford (2*S*)-1-[(cyclohexylmethyl)sulfonyl]-2-piperidinecarboxamide (1.77g) as a colourless oil.

^{1}H-NMR ($CDCl_3$) δ : 4.80 (1H, d), 3.70 (1H, d), 3.20 (1H, t), 2.95 (2H, d), 2.30 (1H, d), 2.00-1.00 (16H, m).

Rotation : $[\alpha]_D^{25}$ = -15.8° (c = 0.1, methanol).

Preparation 27

(2*S*)-1-[(Cyclohexylmethyl)sulfonyl]-2-piperidinecarbonitrile

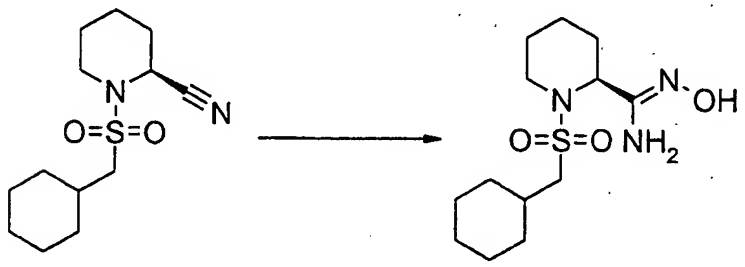


The title compound was prepared by a similar method to Preparation 3 from (2*S*)-1-[(cyclohexylmethyl)sulfonyl]-2-piperidinecarboxamide [see Preparation 26], oxalyl chloride, dimethylformamide and pyridine. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 80:20 changing to 20:80, by volume (in 10% increments), hexane : ethyl acetate to afford (2*S*)-1-[(cyclohexylmethyl)sulfonyl]-2-piperidinecarbonitrile as an oil.

^{1}H-NMR ($CDCl_3$) δ : 4.90 (1H, s), 3.80 (1H, d), 3.00-2.80 (3H, m), 2.00-1.00 (17H, m).

Preparation 28

(Z)-(2S)-1-[Cyclohexylmethylsulfonyl]-N'^{2}-hydroxy-2-piperidinecarboximidamide

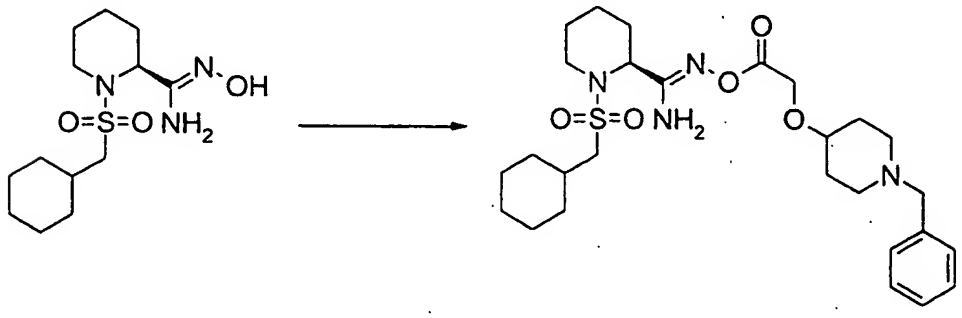


The title compound was prepared by a similar method to Preparation 4 from (2*S*)-1-[(cyclohexylmethyl)sulfonyl]-2-piperidinecarbonitrile [see Preparation 27], hydroxylamine hydrochloride and sodium carbonate. The title compound was obtained as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 7.00 (1H, bs), 5.00 (2H, bs), 4.50 (1H, s), 3.75 (1H, d), 3.05 (1H, d), 2.85 (2H, d), 2.20 (1H, d), 2.00-1.00 (16H, m).

Preparation 29

(Z)-(2S)-N'²-(2-[(1-Benzyl-4-piperidinyl)oxy]acetyloxy)-1-[(cyclohexylmethyl)sulfonyl]-2-piperidinecarboximidamide

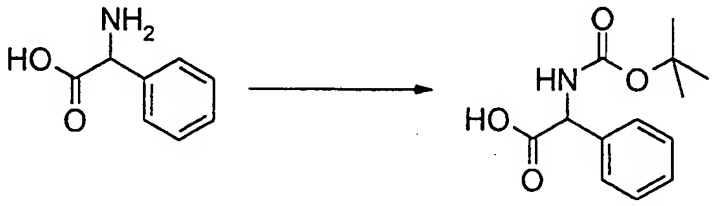


The title compound was prepared by a similar method to Preparation 5 from the compound of Preparation 28, sodium 2-[(1-benzyl-4-piperidyl)oxy]acetate [J.Med.Chem., 1987, 30(8), 999-1003], N-methylmorpholine, 1-hydroxybenzotriazole hydrate and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. The title compound was obtained as a brown liquid.

^{1}H-NMR ($CDCl_3$) δ : 7.30 (5H, m), 5.20 (1H, d), 4.60 (1H, d), 4.30 (2H, s), 3.80 (1H, d), 3.55 (3H, s), 3.10 (1H, m), 2.95 (2H, d), 2.75 (2H, m), 2.35 (1H, d), 2.15 (2H, t), 2.00-1.00 (20H, m).

Preparation 30

alpha-[(*tert*-Butoxycarbonyl)amino]phenylacetic acid

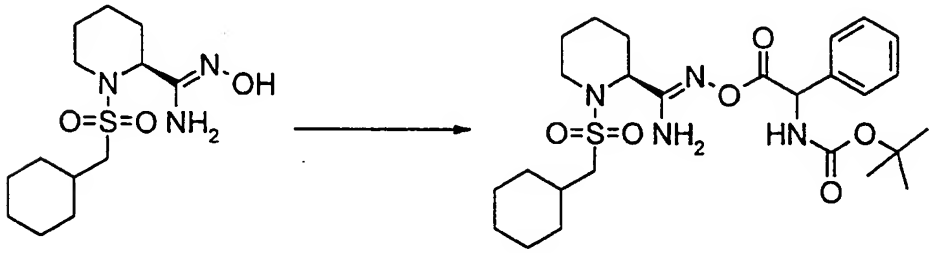


The title compound was prepared by a similar method to Preparation 1 from alpha-aminophenylacetic acid and di-t-butyldicarbonate to afford alpha-[(*tert*-butoxycarbonyl)amino]phenylacetic acid as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 7.40 (5H, m), 5.40-5.10 (1H, bs), 1.50-1.20 (9H, bs).

Preparation 31

tert-Butyl N-(2-[((Z)-amino(2S)-1-[(cyclohexylmethyl)sulfonyl]-2-piperidylmethylidene)amino]oxy-2-oxo-1-phenylethyl)carbamate



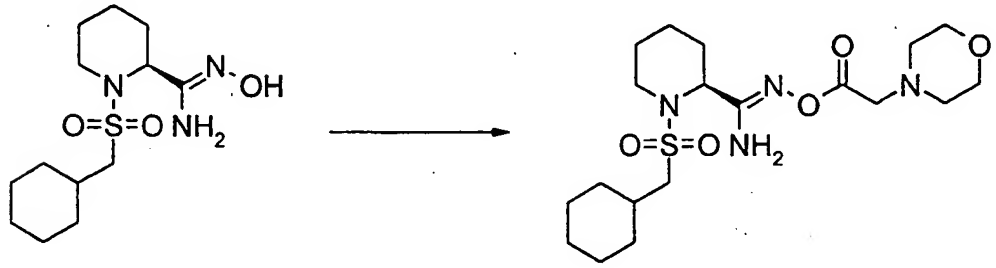
The title compound was prepared by a similar method to Preparation 5 from the compound of Preparation 28 and alpha-[(*tert*-butoxycarbonyl)amino] phenylacetic acid [see Preparation 30]. The crude product was purified

by column chromatography on silica gel eluting with 80:20, by volume, hexane : ethyl acetate to afford the title compound as an oil.

^{1}H-NMR ($CDCl_3$) δ : 7.50 (5H, m), 5.50 (2H, m), 5.20 (2H, bs), 4.60 (1H, s), 3.75 (1H, d), 3.05 (1H, m), 2.90 (2H, s), 2.30 (1H, t), 2.00-1.00 (25H, m).

Preparation 32

(Z)-(2S)-1-[(Cyclohexylmethyl)sulfonyl]-N'^{2}-[(2-morpholinoacetyl)oxy]-2-piperidinecarboximidamide



The title compound was prepared by a similar method to Preparation 5 from the compound of Preparation 28 and 2-morpholinoacetic acid [J.Med.Chem., 1993, 36(3), 320] to afford the title compound (240mg) as a clear oil.

^{1}H-NMR ($CDCl_3$) δ : 5.25 (2H, s), 4.60 (1H, s), 3.80 (5H, m), 3.40 (2H, s), 3.10 (1H, t), 2.95 (2H, d), 2.65 (4H, m), 2.40 (1H, d), 2.00-1.00 (16H, m).

Preparation 33

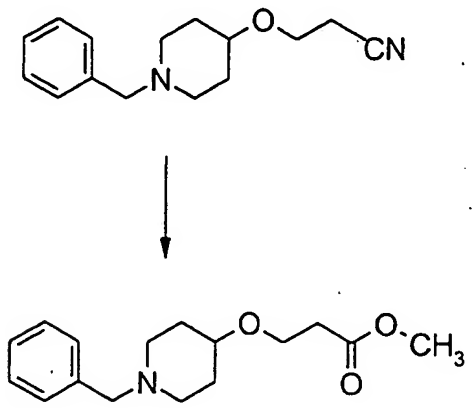
2-[(1-Benzyl-4-piperidyl)oxy]ethyl cyanide

Sodium hydride [50% w/w in mineral oil] (2.0g) was added to a slurry of 1-benzyl-4-piperidinol (400g) and acrylonitrile (530g) at 0°C over 1 hour. The reaction mixture was warmed slowly to room temperature and stirred for 18 hours after which time the acrylonitrile was removed under reduced pressure and the residue taken up in isopropanol (1L). The resulting yellow precipitate was filtered off. The filtrate was evaporated under reduced pressure to afford an orange oil which was dissolved in dichloromethane and washed with water. The organic layer was separated, dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by distillation to afford 2-[(1-benzyl-4-piperidyl)oxy]ethyl cyanide (308g), b.p. 150-160°C @ 0.2mmHg.

^{1}H-NMR ($CDCl_3$) δ : 7.70 (2H, m), 7.45 (3H, m), 4.10 (2H, m), 3.80 (1H, s), 3.65 (2H, t), 3.25 (2H, m), 3.00 (2H, m), 2.60 (4H, m), 2.00 (2H, d).

Preparation 34

Methyl 3-[(1-benzyl-4-piperidyl)oxy]propanoate

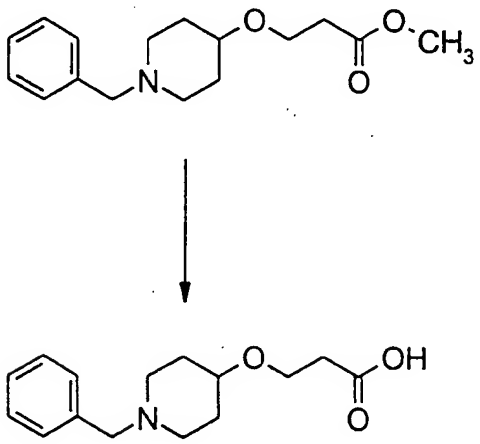


2-[(1-Benzyl-4-piperidyl)oxy]ethyl cyanide (10g) [see Preparation 33] was dissolved in a 20% w/w solution of hydrogen chloride in methanol (100ml). The reaction mixture was then heated under reflux for 3 hours. After this time the mixture was cooled and the white precipitate was filtered off. The filtrate was evaporated under reduced pressure and the residue was dissolved in dichloromethane and washed with aqueous sodium carbonate solution. The organic layer was separated, dried over magnesium sulphate and the solvent was removed under reduced pressure to afford methyl 3-[(1-benzyl-4-piperidyl)oxy]propanoate (7.8g) as an oil.

^{1}H-NMR ($CDCl_3$) δ : 7.30-7.20 (5H, m), 3.75 (5H, m), 3.50 (2H, s), 3.30 (1H, m), 2.75 (2H, m), 2.60 (2H, m), 2.20 (2H, m), 1.90 (2H, m), 1.60 (2H, m).

Preparation 35

3-[(1-Benzyl-4-piperidyl)oxy]propanoic acid

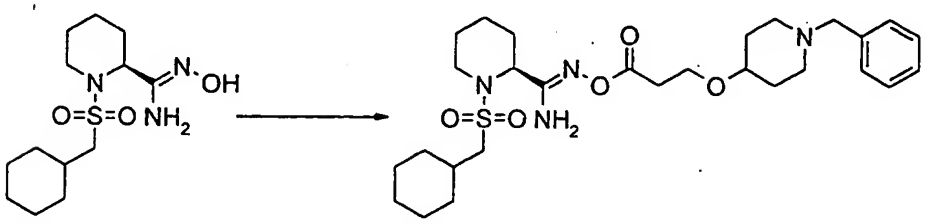


Lithium hydroxide (7.21ml of a 1N aqueous solution) was added to a solution of methyl 3-[(1-benzyl-4-piperidyl)oxy]propanoate (1.00g) [see Preparation 34] in methanol (43.3ml). The reaction mixture was stirred for 36 hours at room temperature after which time the methanol was evaporated under reduced pressure. The crude product was dissolved in a small amount of water and purified on a Dowex 50WX8-200 (trade mark) ion-exchange resin eluting with 0:100 changing to 50:50 (in 10% increments), by volume, water : 0.88 aqueous ammonia solution. The aqueous eluted solution was concentrated under reduced pressure and the residue was frozen and lyophilised to afford 3-[(1-benzyl-4-piperidyl)oxy]propanoic acid (269mg) as an off-white solid.

^{1}H-NMR (d_6-DMSO) δ : 7.30 (5H, m), 3.60 (3H, t), 3.25 (2H, m), 2.60 (2H, m), 2.40 (2H, t), 2.00 (2H, m), 1.80 (2H, m), 1.40 (2H, m).

Preparation 36

(Z)-(2S)-N'²-(3-[1-Benzyl-4-piperidinyl)oxy]propanoyloxy)-1-[(cyclohexylmethyl)sulfonyl]-2-piperidinecarboximidamide

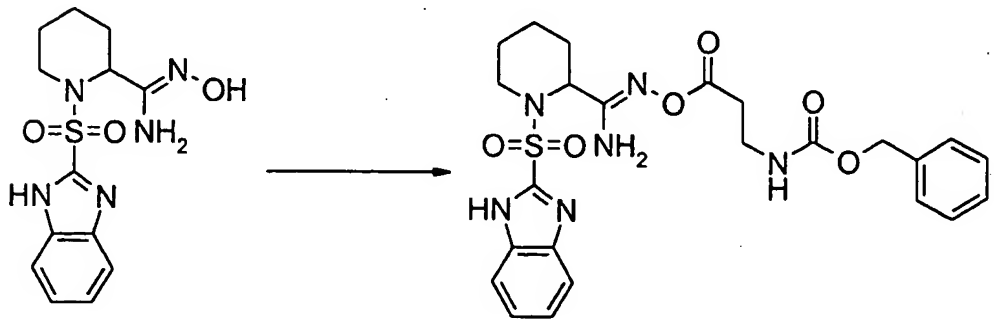


The title compound was prepared by a similar method to Preparation 5 from the compound of Preparation 28 and 3-[(1-benzyl-4-piperidyl)oxy]propanoic acid [see Preparation 35] to afford the title compound as a clear gum.

^{1}H-NMR ($CDCl_3$) δ : 7.30 (5H, m), 5.25 (2H, s), 4.60 (1H, s), 3.80 (3H, m), 3.50 (2H, m), 3.40 (1H, bs), 3.10 (1H, t), 3.00 (2H, m), 2.70 (4H, m), 2.40 (1H, d), 2.10-1.00 (20H, m).

Preparation 37

Benzyl N-3-[((Z)-amino[1-(1H-1,3-benzimidazol-2-ylsulfonyl)-2-piperidyl]methylideneamino)oxy]-3-oxopropylcarbamate

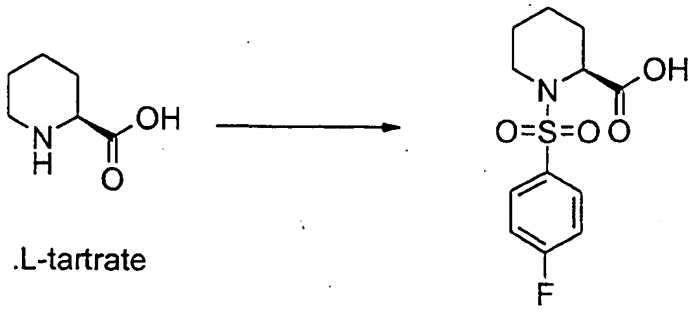


The title compound was prepared by a similar method to Preparation 5 from the compound of Preparation 19 and N-benzyloxycarbonyl-beta-alanine to afford the title compound as an oil.

^{1}H-NMR (d_6-DMSO) δ : 7.70 (2H, d), 7.30 (5H, m), 6.65 (2H, s), 5.05 (2H, s), 4.85 (1H, s), 3.70 (1H, d), 3.30 (1H, t), 3.25 (2H, m), 2.55 (2H, m), 2.05 (1H, d), 1.50 (4H, m), 1.20 (1H, m).

Preparation 38

(2*S*)-1-[(4-Fluorophenyl)sulfonyl]-2-piperidinecarboxylic acid



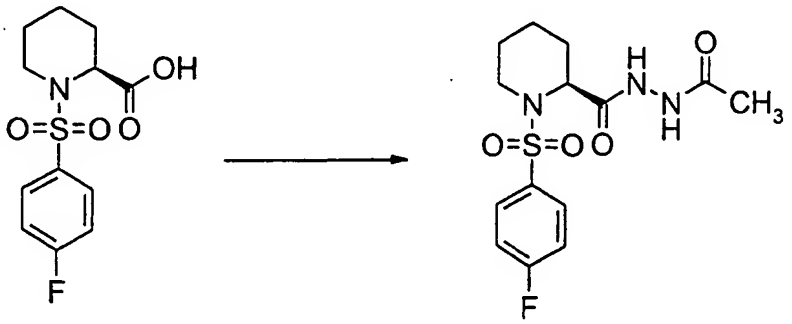
.L-tartrate

(2S)-2-Piperidinecarboxylic acid L-tartrate (10g) [see Preparation 1] was dissolved in 1N aqueous sodium hydroxide solution (107.4ml) and diethylisopropylamine (9.35ml) was added followed by a solution of 4-fluorobenzenesulphonyl chloride (10.45g) in acetone (107ml) at 0°C. The reaction mixture was warmed to room temperature and stirred for 18 hours after which time the solvent was removed under reduced pressure and the residue diluted with 1N aqueous sodium hydroxide solution. The aqueous solution was washed with diethyl ether and acidified with concentrated hydrochloric acid. The product was extracted with ethyl acetate, the organic layers dried over magnesium sulphate and the solvent was removed under reduced pressure to afford (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboxylic acid (9.89g).

^{1}H-NMR (d_6-DMSO) δ : 7.80 (2H, d), 7.40 (2H, d), 4.50 (1H, s), 3.60 (1H, d), 3.20 (1H, t), 2.00 (1H, d), 1.55 (3H, m), 1.20 (2H, m).

Preparation 39

N'2-Acetyl-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarbohydrazide

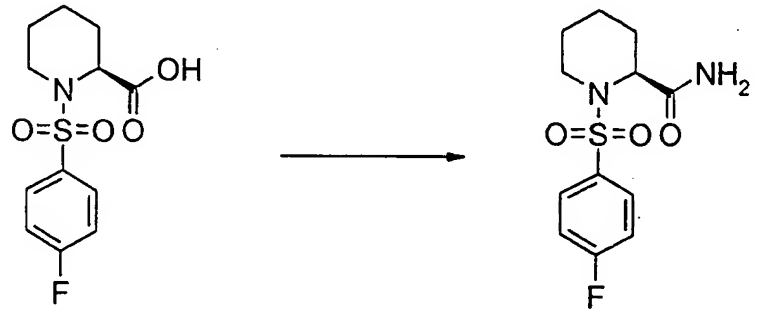


1-Hydroxybenzotriazole hydrate (162mg), acethydrazide (81mg), N-methylmorpholine (275µl) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (230mg) were added to a stirred solution of (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboxylic acid [see Preparation 38] (287mg) in dichloromethane (3ml). The reaction mixture was stirred for 3 hours after which time the mixture was partitioned between dichloromethane and water. The organic layer was separated, dried over magnesium sulphate and the solvent removed under reduced pressure to afford *N*'2-acetyl-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarbohydrazide (340mg) as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 8.00 (2H, d), 7.20 (2H, d), 4.60 (1H, d), 3.90 (1H, d), 3.40 (1H, t), 2.25 (1H, d), 2.05 (3H, s), 1.50-1.00 (5H, m).

Preparation 40

(2*S*)-1-[(4-Fluorophenyl)sulfonyl]-2-piperidinecarboxamide



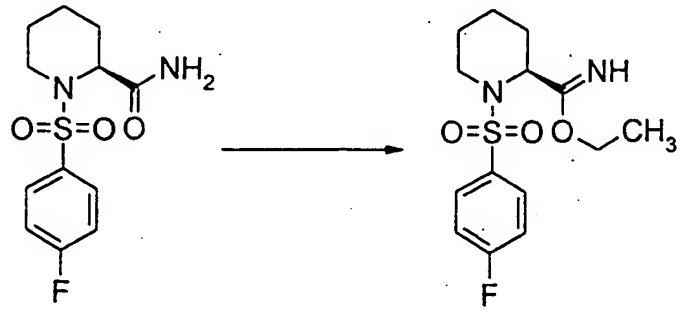
The title compound was prepared by a similar method to Preparation 2 from (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboxylic acid [see Preparation 38]. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 50:50 changing to 0:100 (in 10% increments), by volume, hexane : ethyl acetate to afford (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboxamide as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 8.00 (2H, d), 7.40 (2H, d), 6.60 (1h, bs), 5.50 (1H, bs), 4.60 (1H, d), 4.00 (1H, d), 3.20 (1H, t), 2.25 (1H, d), 1.50 (3H, m), 1.10 (2H, m).

Rotation : $[\alpha]_D^{25}$ = -43.01° (c = 0.1, methanol).

Preparation 41

Ethyl (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboximidate

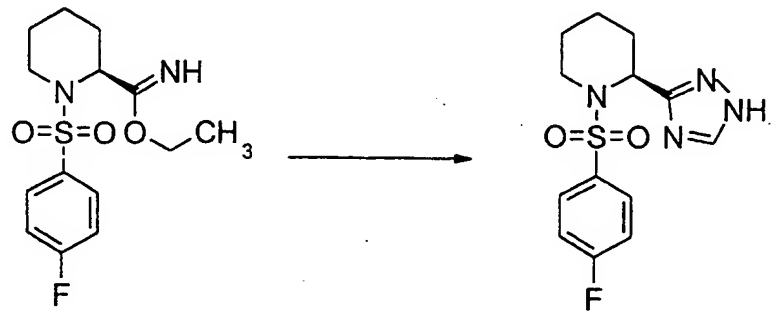


(2*S*)-1-[(4-Fluorophenyl)sulfonyl]-2-piperidinecarboxamide (286mg) [see Preparation 40] was added to a solution of triethyloxonium hexafluorophosphate (304mg) in dichloromethane (5ml). The reaction mixture was stirred at room temperature for 18 hours after which time the mixture was diluted with dichloromethane and washed with saturated aqueous sodium hydrogen carbonate solution. The organic layer was separated, dried over magnesium sulphate and the solvent was removed under reduced pressure to afford ethyl (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboximidate (290mg).

^{1}H-NMR ($CDCl_3$) δ : 7.90 (2H, d), 7.20 (2H, d), 4.70 (1H, d), 4.20 (2H, m), 3.80 (1H, d), 3.10 (1H, t), 2.20 (1H, d), 1.60-1.20 (8H, m).

Preparation 42

(2*S*)-1-[(4-Fluorophenyl)sulfonyl]-2-(1*H*-1,2,4-triazol-3-yl)piperidine

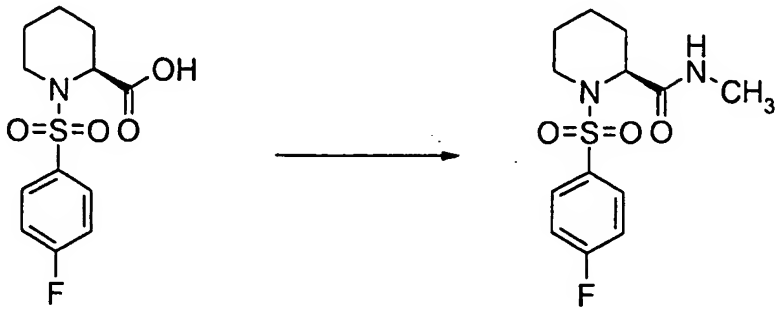


Formylhydrazine (120mg) was added to a solution of ethyl (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboximidate (295mg) [see Preparation 41] in toluene (5ml) and 1,4-dioxane (5ml). The reaction mixture was stirred at reflux for 26 hours after which time the solvent was removed under reduced pressure. The residue was diluted with ethyl acetate and washed with water. The organic layer was separated, dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 100:0 changing to 0:100 (in 10% increments), by volume, hexane:ethyl acetate to afford (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-(1*H*-1,2,4-triazol-3-yl)piperidine (95mg) as an off-white foam.

^{1}H-NMR ($CDCl_3$) δ : 8.05 (1H, s), 7.80 (2H, d), 7.10 (2H, t), 5.40 (1H, bs), 3.75 (1H, d), 3.20 (1H, t), 2.30 (1H, d), 1.80-1.40 (5H, m).

Preparation 43

*N*2-Methyl-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboxamide



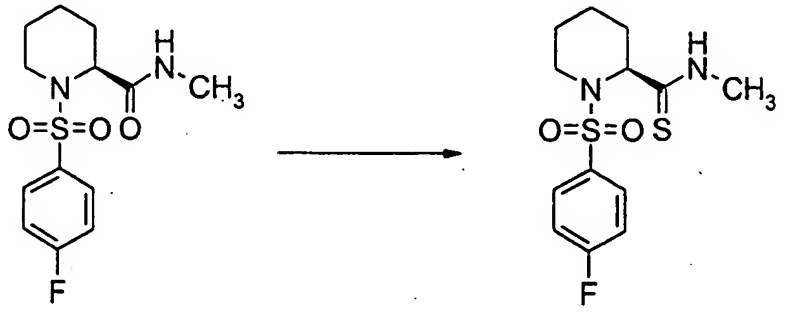
The title compound was prepared by a similar method to Preparation 39 from (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboxylic acid [see Preparation 38] and methylamine to afford *N*2-methyl-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboxamide as an oil.

^{1}H-NMR ($CDCl_3$) δ : 7.90 (2H, t), 7.20 (2H, m), 6.60 (1H, bs), 4.45 (1H, s), 3.90 (1H, d), 3.10 (1H, t), 2.85 (3H, s), 2.30 (1H, d), 1.45 (3H, m), 1.10 (2H, m).

Rotation : $[\alpha]_D^{25}$ = -44.4° (c = 0.1, methanol).

Preparation 44

*N*2-Methyl-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarbothioamide



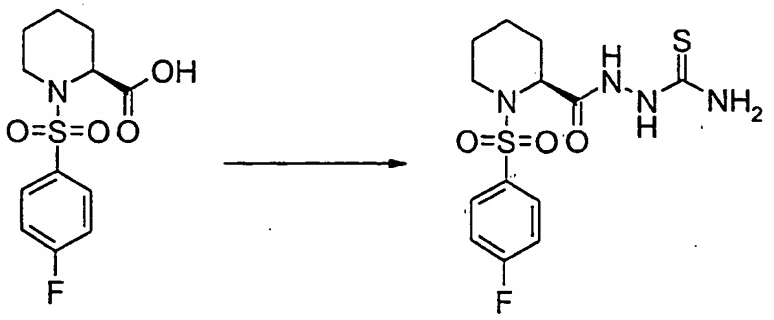
The title compound was prepared by a similar method to Example 20 from *N*2-methyl-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboxamide [see Preparation 43] and Lawesson's reagent. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 0:100 changing to 25:75 (in 5% increments), by volume, ethyl acetate : hexane, to

afford *N*2-methyl-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarbothioamide as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 8.60 (1H, bs), 7.90 (2H, t), 7.30 (2H, m), 4.65 (1H, s), 3.95 (1H, d), 3.30 (3H, d), 2.95 (2H, d), 1.45 (3H, m), 1.10 (2H, m).

Preparation 45

2-((2*S*)-1-[(4-Fluorophenyl)sulfonyl]-2-piperidylcarbonyl)-1-hydrazinecarbothioamide

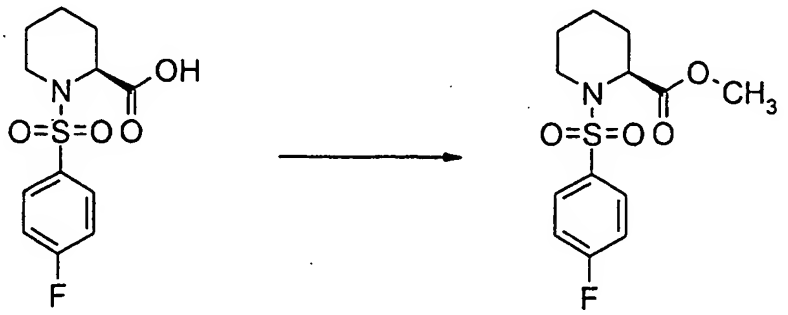


1,1'-Carbonyldimidazole (195mg) was added to a solution of (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboxylic acid (287mg) [see Preparation 38] in tetrahydrofuran (5ml). The reaction mixture was stirred and heated under reflux for 1 hour and then evaporated under reduced pressure to afford a yellow gum. The gum was dissolved in 1,4-dioxane (5ml) and thiosemicarbazide (182mg) was added. The reaction mixture was heated under reflux for 1.25 hour. After this time the cooled mixture was purified by column chromatography on MCI (trade mark) reverse phase gel eluting with a solvent gradient of 30:70 changing to 70:30, by volume, methanol : water to afford 2-((2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidylcarbonyl)-1-hydrazinecarbothioamide (178mg) as a white foam.

^{1}H-NMR (d_6-DMSO) δ : 9.90 (1H, bs), 9.20 (1H, bs), 7.80 (2H, d), 7.40 (2H, d), 4.60 (1H, s), 3.60 (1H, m), 3.40 (1H, m), 2.10 (1H, d), 1.60-1.00 (5H, m).

Preparation 46

Methyl (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboxylate

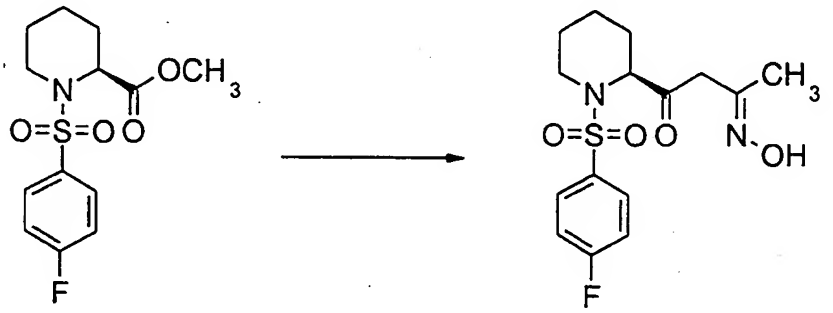


4-Dimethylaminopyridine (61mg), methanol (45μl) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (192mg) were added to a solution of (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboxylic acid (287mg) [see Preparation 38] in dichloromethane (6ml). The reaction mixture was stirred at room temperature for 56 hours after which time it was diluted with dichloromethane and washed with 1N aqueous hydrochloric acid solution followed by saturated aqueous sodium hydrogen carbonate solution. The organic layer was dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 90:10 changing to 50:50, by volume, hexane : ethyl acetate, to afford methyl (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboxylate (239mg) as an oil.

^{1}H-NMR ($CDCl_3$) δ : 7.80 (2H, t), 7.10 (2H, t), 4.70 (1H, d), 3.70 (1H, d), 3.50 (3H, s), 3.20 (1H, t), 2.10 (1H, d), 1.80-1.20 (5H, m).

Preparation 47

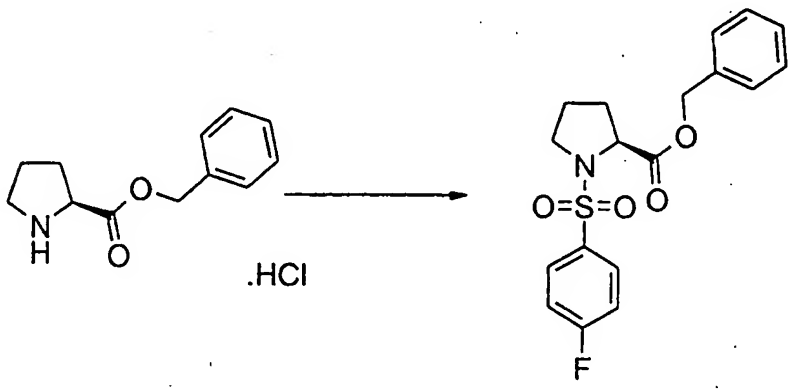
1-(2S)-1-[(4-Fluorophenyl)sulfonyl]-2-piperidyl-1,3-butanedione 3-oxime



n-Butyllithium (1.98ml) [1.6M in hexane] was added dropwise to a solution of acetone oxime (116mg) in tetrahydrofuran (5ml) at 0°C. The reaction mixture was stirred for 1 hour at 0°C and a solution of methyl (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboxylate (239mg) [see Preparation 46] in tetrahydrofuran (1.5ml) was added. The mixture was stirred for 4 hours after which time saturated aqueous ammonium chloride solution (3ml) was added. The mixture was partitioned between dichloromethane and aqueous ammonium chloride solution, the aqueous phase was separated and acidified with 1N aqueous hydrochloric acid solution and the product was extracted with dichloromethane. The organic layer was separated , dried over magnesium sulphate, and the solvent removed under reduced pressure to afford the title compound (211mg). The crude product was used without further purification.

Preparation 48

Benzyl (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-pyrrolidinecarboxylate



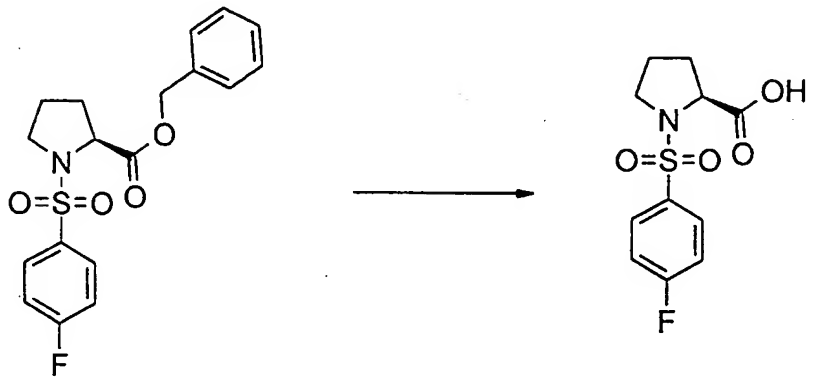
The title compound was prepared by a similar method to Example 1 from L-proline benzyl ester hydrochloride and 4-fluorobenzenesulphonyl chloride. The crude product was purified by column chromatography on silica gel eluting with dichloromethane to afford benzyl (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-pyrrolidinecarboxylate as a clear oil.

^{1}H-NMR ($CDCl_3$) δ : 7.90 (2H, m), 7.40 (5H, m), 7.20 (2H, t), 5.10 (2H, s), 4.45 (1H, m), 3.40 (2H, m), 2.20-1.80 (4H, m).

Rotation : $[\alpha]_D^{25}$ = -93.62° (c = 0.1, methanol).

Preparation 49

(2*S*)-1-[(4-Fluorophenyl)sulfonyl]-2-pyrrolidinecarboxylic acid



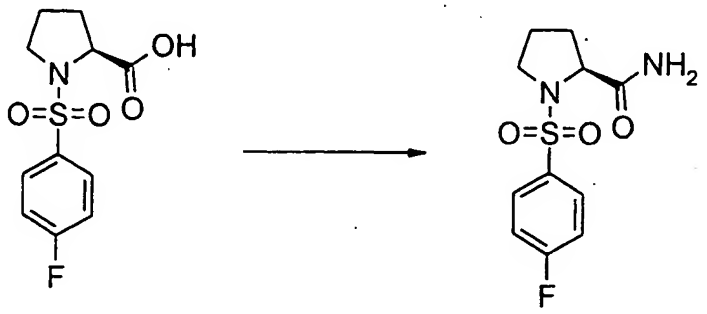
Benzyl (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-pyrrolidinecarboxylate (10.03g) [see Preparation 48] was dissolved in ethanol (200ml) and hydrogenated over 10% w/w palladium-on-charcoal (2.0g) at 60psi (414kPa) for 18 hours. The reaction mixture was then filtered through a plug of ARBOCEL (trade mark) filter aid and the filtrate evaporated under reduced pressure. The residue was azeotroped with dichloromethane to afford (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-pyrrolidinecarboxylic acid (5.50g) as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 8.00 (2H, t), 7.20 (2H, t), 4.40 (1H, s), 3.50 (1H, m), 3.30 (1H, m), 2.20-2.00 (3H, m), 1.80 (1H, m).

Rotation : $[\alpha]_D^{25}$ = -92.62° (c = 0.1 methanol).

Preparation 50

(2*S*)-1-[(4-Fluorophenyl)sulfonyl]-2-pyrrolidinecarboxamide

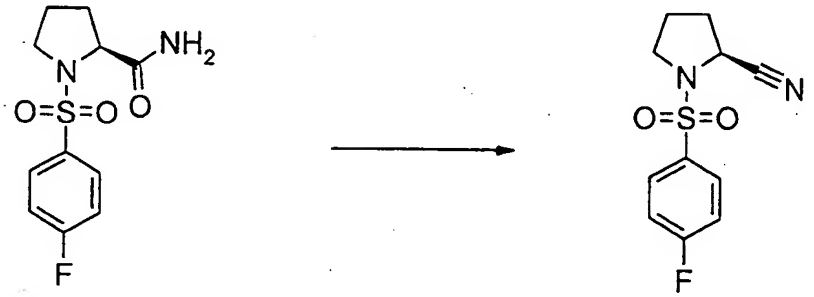


The title compound was prepared by a similar method to Preparation 2 from (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-pyrrolidinecarboxylic acid [see Preparation 49] to afford (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-pyrrolidinecarboxamide as an oil.

^{1}H-NMR ($CDCl_3$) δ : 7.85 (2H, m), 7.20 (2H, t), 6.80 (1H, bs), 5.60 (1H, bs), 4.00 (1H, t), 3.60 (1H, m), 3.10 (1H, m), 2.20 (1H, m), 1.80 (1H, m), 1.60 (2H, m).

Preparation 51

(2*S*)-1-[(4-Fluorophenyl)sulfonyl]-2-pyrrolidinecarbonitrile



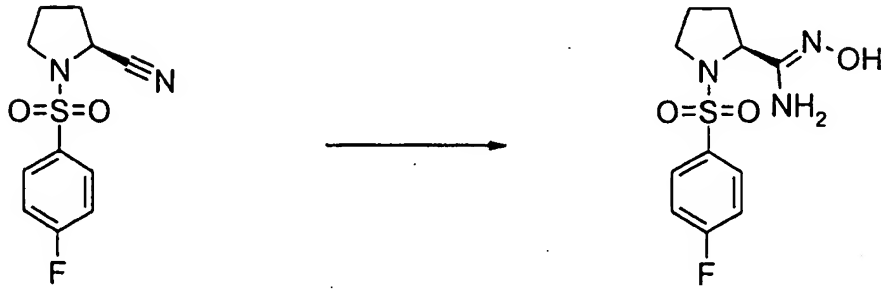
The title compound was prepared by a similar method to Preparation 3 from (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-pyrrolidinecarboxamide [see Preparation 50] and oxalyl chloride. The crude product was purified by column chromatography on silica gel eluting with dichloromethane to afford (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-pyrrolidinecarbonitrile as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 7.90 (2H, m), 7.20 (2H, t), 4.60 (1H, m), 3.40 (1H, m), 3.25 (1H, m), 2.25-2.00 (4H, m).

Rotation : $[\alpha]_D^{25}$ = -118° (c = 0.1, methanol).

Pr parati n 52

(Z)-(2S)-1-[(4-Fluorophenyl)sulfonyl]-N'²-hydroxy-2-pyrrolidinecarboximidamide



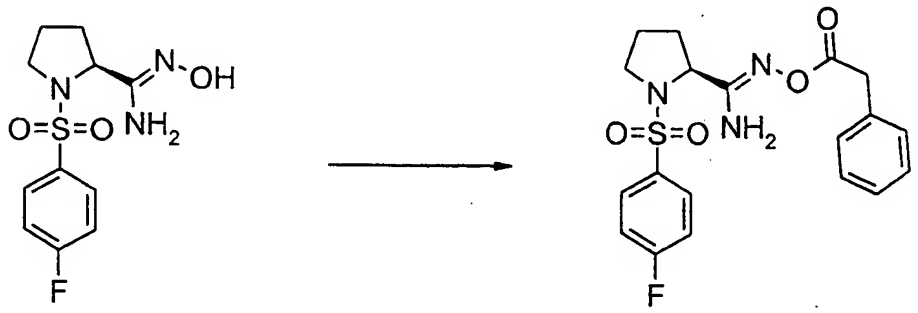
The title compound was prepared by the method of Preparation 4 from (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-pyrrolidinecarbonitrile [see Preparation 51] and hydroxylamine hydrochloride to afford the title compound as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 7.90 (2H, m), 7.30 (2H, t), 6.50 (1H, bs), 5.00 (2H, bs), 4.10 (1H, m), 3.60 (1H, m), 3.20 (1H, m), 2.20 (1H, m), 2.00 (1H, m), 1.60 (2H, m).

Rotation : $[\alpha]_D^{25}$ = -124.22° (c = 0.1, methanol).

Preparation 53

(Z)-(2S)-1-[(4-Fluorophenyl)sulfonyl]-N'²-[(2-phenylacetyl)oxy]-2-pyrrolidinecarboximidamide

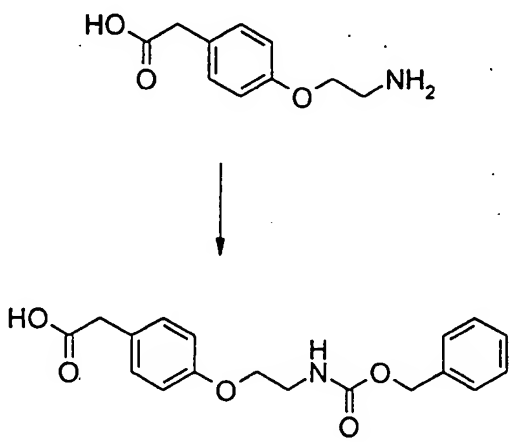


Saturated aqueous sodium hydrogen carbonate solution (10ml) was added to a solution of the compound of Preparation 52 (250mg) in dichloromethane (10ml), followed by phenylacetyl chloride (127µl). The reaction mixture was stirred at room temperature for 1hour after which time the mixture was diluted with dichloromethane. The organic layer was separated , dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with 90:10 changing to 70:30 (in 10% increments), by volume, dichloromethane : ethyl acetate, to afford the title compound (186mg) as a white foam.

^{1}H-NMR ($CDCl_3$) δ : 7.90 (2H, m), 7.40-7.10 (7H, m), 5.10 (2H, bs), 4.20 (1H, m), 3.80 (2H, s), 3.60 (1H, m), 3.20 (1H, q), 2.25 (1H, m), 1.90 (1H, m), 1.80-1.60 (2H, m).

Preparation 54

2-[4-(2-[Benzyloxycarbonylamino]ethoxy)phenyl]acetic acid

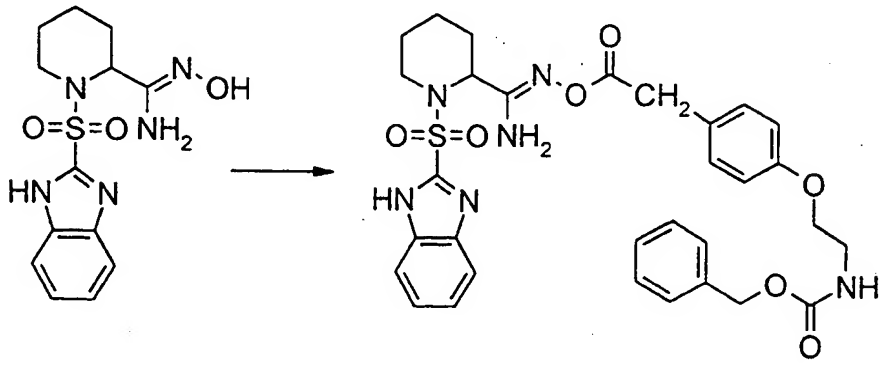


Sodium hydroxide (222mg) was added to a solution of 2-[4-(2-aminoethoxy)-phenyl]acetic acid (394mg) (see DE-A-2250400) in 1,4-dioxane : water (1:1, by volume) (20ml) at 0°C. The reaction mixture was stirred for 20 minutes then benzyl chloroformate (319mg) was added to the mixture and the solution was stirred for 4 hours. Additional benzyl chloroformate (70mg) was added to the reaction mixture and it was stirred for a further 1 hour. The solvent was removed under reduced pressure. The resulting solid was dissolved in water and washed with diethyl ether. The aqueous layer was acidified with 2N aqueous hydrochloric acid solution and the product was extracted with ethyl acetate. The organic solution was dried over magnesium sulphate and the solvent removed under reduced pressure to afford 2-[4-(2-[benzyloxycarbonylamino]ethoxy)phenyl]acetic acid (375mg) as a solid.

^{1}H-NMR ($CDCl_3$) δ : 7.40 (5H, m), 7.20 (2H, d), 6.90 (2H, d), 5.25 (1H, bs), 5.15 (2H, s), 4.05 (2H, s), 3.60 (4H, s).

Preparation 55

Benzyl N-[2-(4-2-[((Z)-amino[1-(1H-1,3-benzimidazol-2-ylsulfonyl)-2-piperidyl]methylideneamino)oxy]-2-oxoethylphenoxy)ethyl]carbamate

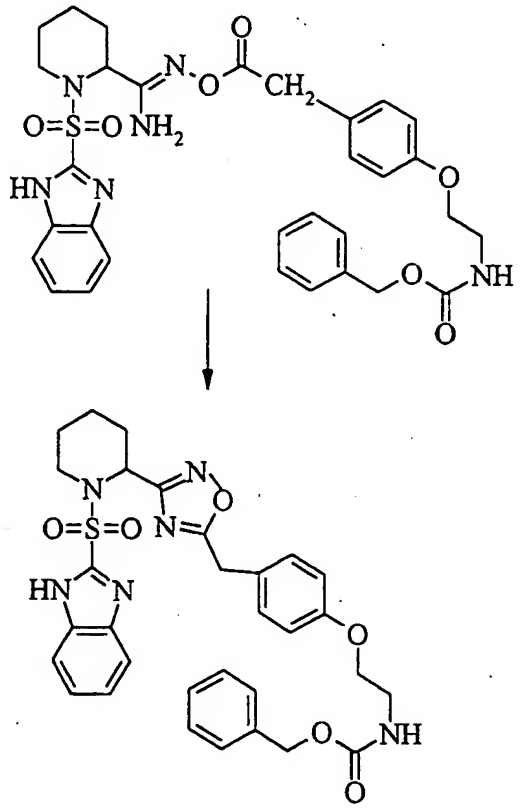


2-[4-(2-(Benzyloxycarbonylamino]ethoxy)phenyl]acetic acid (350mg) [see Preparation 54] was dissolved in dichloromethane (10ml) and the compound of Preparation 19 (323mg) was added followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (230mg) and N-methylmorpholine (132µl). The reaction mixture was stirred for 56 hours after which time the crude mixture was purified by column chromatography on silica gel eluting with 100:0 changing to 60:40, by volume, hexane:ethyl acetate (in 10% increments), to afford the title compound (384mg) as an oil.

^{1}H-NMR ($CDCl_3$) δ : 7.85 (2H, bs), 7.40-7.20 (9H, m), 6.90 (2H, d), 5.20 (3H, bs), 5.15 (2H, s), 4.90 (1H, m), 4.10 (2H, m), 3.80 (2H, s), 3.65 (2H, q), 3.50 (1H, d), 3.30 (1H, m), 2.10 (1H, m), 1.90 (1H, m), 1.80-1.50 (4H, m).

Preparation 56

Benzyl *N*-(2-[4-(3-[1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethyl)phenoxy]ethyl)carbamate

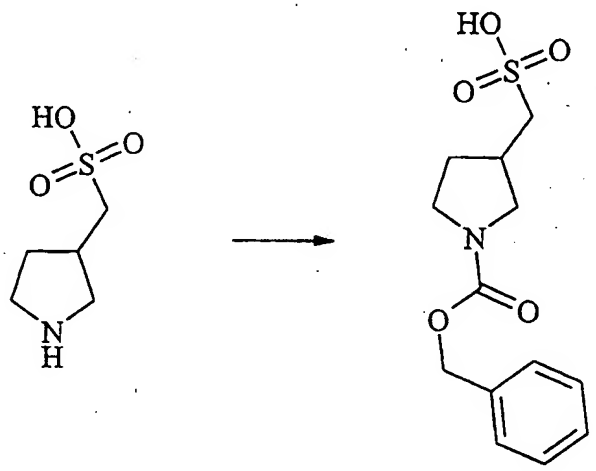


The title compound was prepared by a similar method to Example 16 from the compound of Preparation 55 and pyridine. The crude product was purified by column chromatography on silica gel eluting with 100:0 changing to 60:40, by volume, hexane:ethyl acetate (in 10% increments) to afford benzyl *N*-(2-[4-(3-[1-(1*H*-benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethyl)phenoxy]ethyl)carbamate as an oil.

^{1}H-NMR ($CDCl_3$) δ : 7.80 (1H, d), 7.40-7.20 (8H, m), 7.05 (2H, d), 6.80 (2H, d), 5.50 (1H, d), 5.20 (1H, bs), 5.10 (2H, s), 4.00 (3H, m), 3.85 (2H, s), 3.60 (2H, m), 3.20 (1H, m), 2.30 (1H, d), 2.10 (1H, m), 1.80-1.60 (4H, m).

Preparation 57

1-[(Benzyloxy)carbonyl]-3-pyrrolidinylmethanesulfonic acid

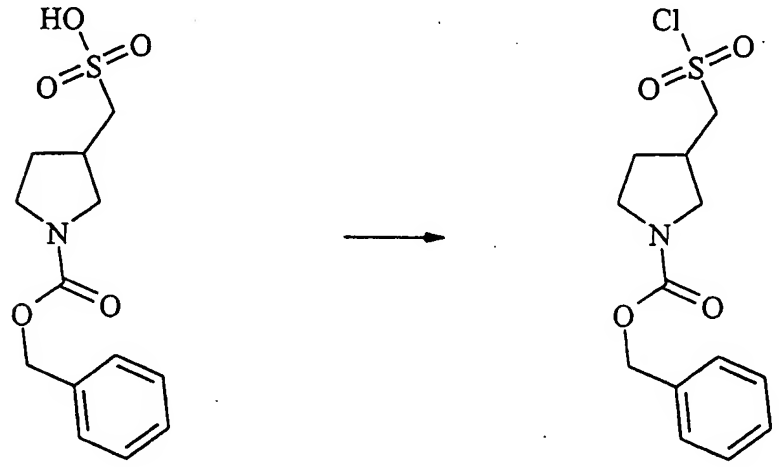


1*H*-3-Pyrrolidinylmethanesulfonic acid (1.55g) [Labouta, Ibrahim M, et al Acta Chem Scand, Ser B, (1982), B36(10), 669-74] was dissolved in dioxan (20ml) and 1N aqueous sodium hydroxide (40ml) was added followed by benzyl chloroformate (1.62ml). The reaction mixture was stirred at room temperature for 1hr, after which time the solvent was removed under reduced pressure and the residue partitioned between dichloromethane and water. The aqueous phase was separated and acidified with conc. aqueous hydrochloric acid, the product was then extracted with ethyl acetate. The organic layer was dried over magnesium sulphate and the solvent removed under reduced pressure to afford 1-[(benzyloxy)carbonyl]-3-pyrrolidinylmethanesulfonic acid (2.20g) as a gum.

^{1}H-NMR (D_2O) δ : 7.35 (5H, m), 5.05 (2H, s), 3.65 (1H, m), 3.60 (1H, m), 3.30 (1H, m), 3.10 (1H, m), 2.90 (2H, m), 2.55 (1H, m), 2.10 (1H, m), 1.60 (1H,m).

Preparation 58

Benzyl 3-(chlorosulfonylmethyl)-1-pyrr lidinecarboxylate

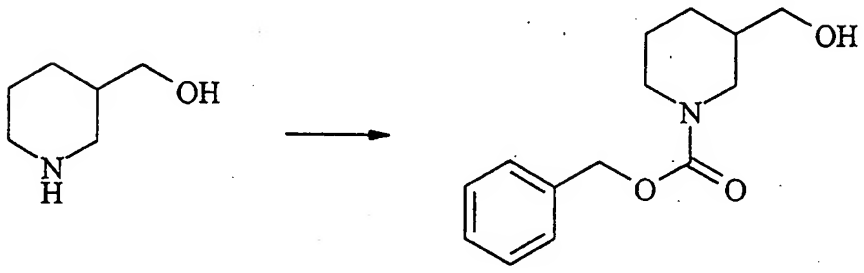


Thionyl chloride (5ml) was added to a solution of 1-[(benzyloxy)carbonyl]-3-pyrrolidinylmethanesulfonic acid (600mg) [Preparation 57] in dimethylformamide (50ml). The reaction mixture was heated to reflux for 20mins after which time the cooled mixture was evaporated to dryness. The residue was partitioned between ethyl acetate and water. The organic layer was separated, dried over magnesium sulphate and the solvent removed under reduced pressure to afford benzyl 3-(chlorosulfonylmethyl)-1-pyrrolidinecarboxylate (560mg) as an oil.

^{1}H-NMR ($CDCl_3$) δ : 7.35 (5H, m), 5.15 (2H, s), 3.90 (1H, m), 3.80 (2H, m), 3.60 (1H, m), 3.40 (1H, m), 3.20 (1H, t), 2.90 (1H, m), 2.30 (1H, bs), 1.80 (1H, m).

Preparation 59

Benzyl 3-(hydroxymethyl)-1-piperidin carboxylate

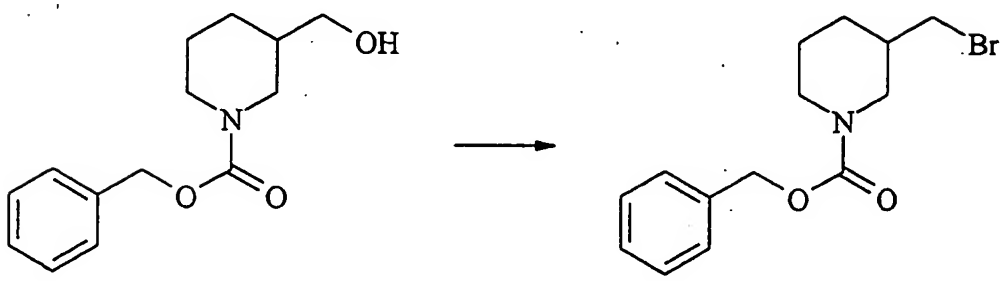


Benzyl chloroformate (7.88ml) was added over ten minutes to an ice-cold solution of 3-hydroxymethyl piperidine (5.76g) and ethyldiisopropylamine (9.58ml) in dichloromethane (300ml). The reaction mixture was allowed to warm to room temperature and stirred for 1 hr. The reaction was then diluted with dichloromethane (500ml), washed with 1N aqueous hydrochloric acid (200ml), dried over magnesium sulphate, and evaporated to afford benzyl 3-(hydroxymethyl)-1-piperidinecarboxylate as an oil (12.4g).

^{1}H-NMR (d6-DMSO) δ : 7.30 (5H, m), 5.00 (2H, s), 4.45 (1H, t), 4.00 (1H, d), 3.85 (1H, d), 3.25 (2H, m), 3.15 (1H, m), 2.75 (1H, bs), 1.60 (2H, m), 1.50 (1H, m), 1.30 (1H, m), 1.10 (1H, m).

Preparation 60

Benzyl 3-(bromomethyl)-1-piperidinecarboxylate

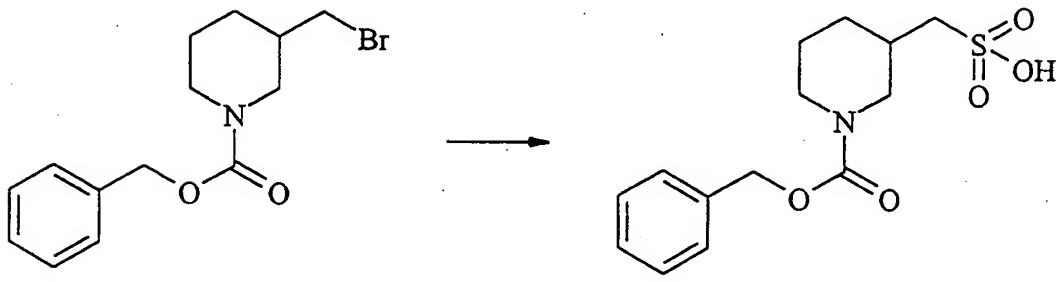


The title compound was prepared by the method of Preparation 9 from benzyl 3-(hydroxymethyl)-1-piperidinecarboxylate [Preparation 59] and carbon tetrabromide. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 0:100 changing to 80:20, by volume ethyl acetate : hexane, in 10% increments, to afford benzyl 3-(bromomethyl)-1-piperidinecarboxylate as an oil.

^{1}H-NMR (d6-DMSO) δ : 7.30 (5H, m), 5.00 (2H, s), 4.05 (1H, d), 3.80 (1H, d), 3.40 (2H, m), 2.80-2.60 (2H, m), 1.80 (1H, m), 1.75 (1H, m), 1.60 (1H, m), 1.40 (1H, m), 1.20 (1H, m).

Preparation 61

1-[(Benzyloxy)carbonyl]-3-piperidylmethanesulfonic acid

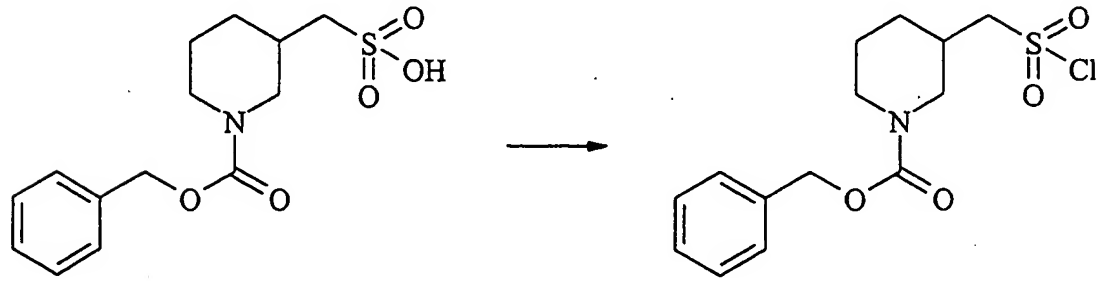


Sodium sulphite (12.6g) in water (25ml) was added to a stirred solution of benzyl 3-(bromomethyl)-1-piperidinecarboxylate (7.8g) [Preparation 60] in dioxan (25ml). The reaction mixture was stirred at reflux for 18hrs, after which time the solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The aqueous solution was separated and acidified with 2N aqueous hydrochloric acid. The product was then extracted with ethyl acetate, dried over magnesium sulphate and the solvent removed under reduced pressure to afford 1-[(benzyloxy)carbonyl]-3-piperidylmethanesulfonic acid as a hygroscopic solid (4.5g).

^{1}H-NMR (d6-DMSO) δ : 7.30-7.25 (5H, m), 5.00 (2H, s), 4.20 (1H, d), 4.00 (1H, m), 3.80-3.20 (2H, m), 2.80 (1H, m), 2.15 (1H, d), 1.90 (1H, s), 1.80 (1H, m), 1.55 (1H, m), 1.30 (1H, m), 1.10 (1H, m).

Preparation 62

Benzyl 3-[(chlorosulfonyl)methyl]-1-piperidinecarboxylate

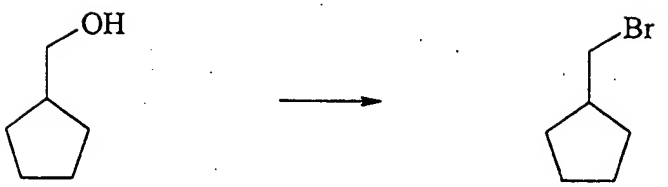


The title compound was prepared by the method of Preparation 58 from 1-[(benzyloxy)carbonyl]-3-piperidylmethanesulfonic acid [see Preparation 61]and thionyl chloride to afford benzyl 3-[(chlorosulfonyl)methyl]-1-piperidinecarboxylate as an oil.

^{1}H-NMR ($CDCl_3$) δ : 7.30 (5H, m), 5.10 (2H, s), 4.00 (1H, d), 3.75 (1H, m), 3.70-3.55 (2H, m), 3.20-3.05 (2H, m), 2.45 (1H, m), 2.10 (1H, m), 1.80-1.50 (3H, m).

Preparation 63

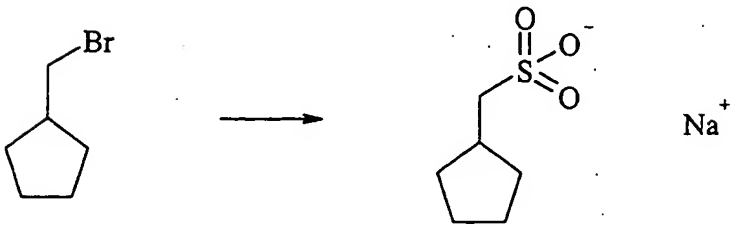
1-(Bromomethyl)cyclopentane



The subtitle compound was prepared by the method of Preparation 9 from cyclopentylmethanol and carbon tetrabromide. The crude product was purified by fractional distillation b.pt. 80°C @ 30mmHg to afford 1-(bromomethyl)cyclopentane as a colourless oil.

Preparation 64

Sodium cyclopentylmethanesulfonate

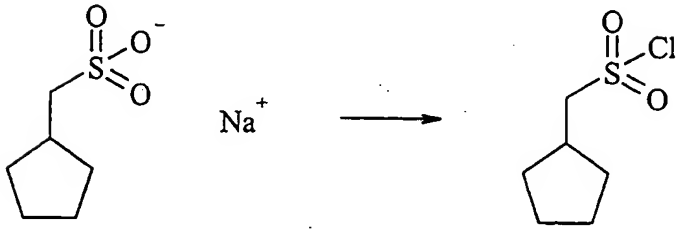


The subtitle compound was prepared by the method of Preparation 61 from 1-(bromomethyl)cyclopentane [Preparation 63] and sodium sulphite. The crude product was purified by recrystallisation from water to afford sodium cyclopentylmethanesulfonate as a white solid.

^{1}H-NMR (D_2O) δ : 2.85 (2H, d), 2.10 (1H, m), 1.80 (2H, m), 1.60-1.40 (4H, m), 1.20 (2H, m).

Preparation 65

Cyclopentylmethanesulfonyl chloride

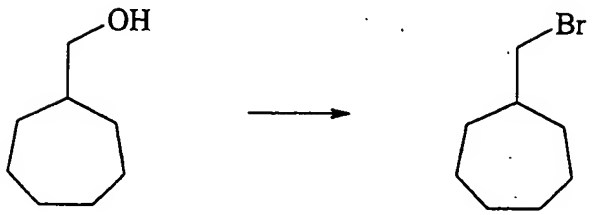


The subtitle compound was prepared by the method of Preparation 58 from sodium cyclopentylmethanesulfonate [Preparation 64] and thionyl chloride, to afford cyclopentylmethanesulfonyl chloride as a solid.

^{1}H-NMR ($CDCl_3$) δ : 3.75 (2H, d), 2.60 (1H, m), 2.05 (2H, m), 1.80-1.60 (4H, m), 1.40 (2H, m).

Preparation 66

1-(Bromomethyl)cycloheptane

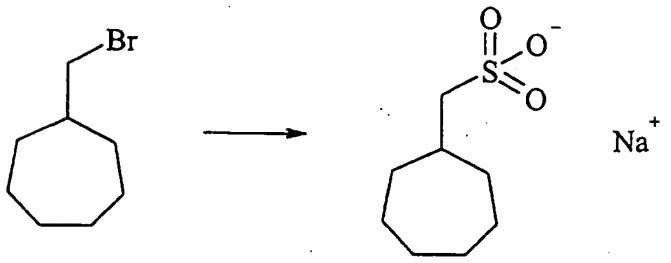


The subtitle compound was prepared by the method of Preparation 9 from cycloheptylmethanol and carbon tetrabromide. The crude product was purified by fractional distillation, b.pt. 115°C - 120°C @ 30mmHg to afford 1-(bromomethyl)cycloheptane as an oil.

^{1}H-NMR ($CDCl_3$) δ : 3.25 (2H, d), 1.80 (2H, m), 1.70-1.20 (11H, m).

Preparation 67

Sodium cycloheptylmethanesulfonate

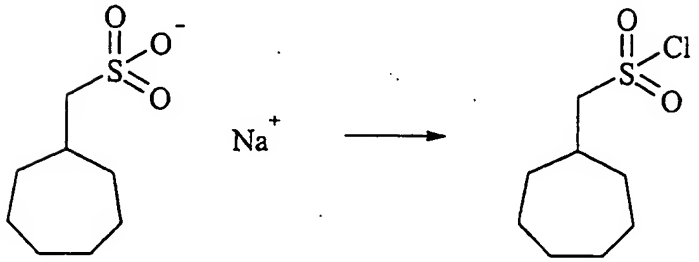


The subtitle compound was prepared by the method of Preparation 61 from 1-(bromomethyl)cycloheptane [Preparation 66] and sodium sulfite. The crude product was purified by recrystallisation from water to afford sodium cycloheptylmethanesulfonate as a white solid.

^{1}H-NMR (D_2O) δ : 2.75 (2H, d), 1.90 (1H, m), 1.75 (2H, m), 1.60-1.20 (10H, m).

Preparation 68

Cycloheptylmethanesulfonyl chloride

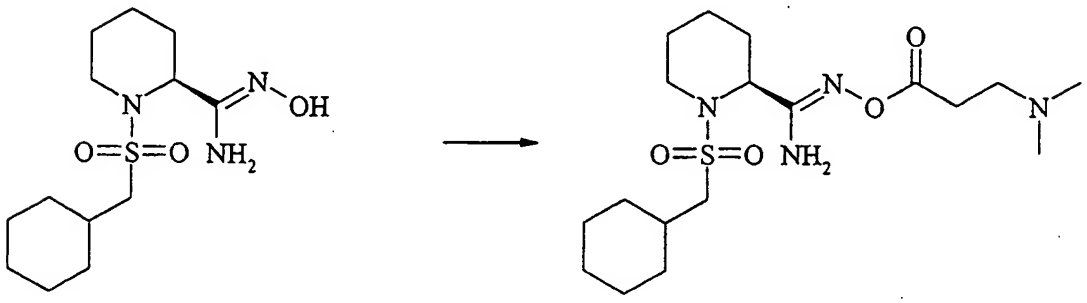


The subtitle compound was prepared by the method of Preparation 58 from sodium cycloheptylmethanesulfonate [Preparation 67] and thionyl chloride, to afford cycloheptylmethanesulfonyl chloride as a colourless oil.

^{1}H-NMR ($CDCl_3$) δ : 3.65 (2H, d), 2.40 (1H, m), 2.00 (2H, m), 1.70-1.40 (10H, m).

Preparation 69

(Z)-(2S)-1-[(Cyclohexylmethyl)sulfonyl]-N'^2-[3-(dimethylamino)propanoyl]oxy-2-piperidinecarboximidamide

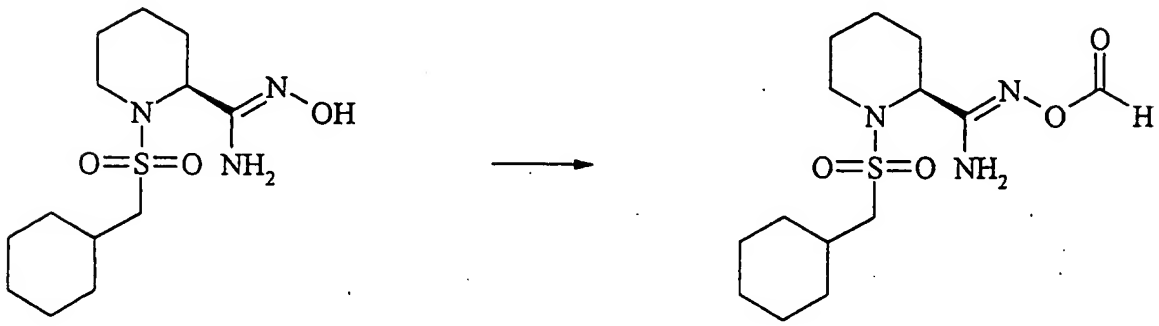


The title compound was prepared by the method of Preparation 5 from (Z)-(2S)-1-[cyclohexylmethylsulfonyl]-N'^{2}-hydroxy-2-piperidinecarboximidamide [see Preparation 28], 3-(dimethylamino)propanoic acid [Papapoulos, et al, WO 9619998A1], N-methyl morpholine, hydroxybenzotriazole hydrate and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, to afford (Z)-(2S)-1-[(cyclohexylmethyl)sulfonyl]-N'^2-[3-(dimethylamino)propanoyl]oxy-2-piperidinecarboximidamide as an oil.

^{1}H-NMR ($CDCl_3$) δ : 4.60 (1H, d), 3.75 (1H, d), 3.20 (1H, t), 2.90 (2H, m), 2.60 (4H, m), 2.30 (1H, d), 2.25 (6H, s), 2.00 (4H, m), 1.80-1.60 (6H, m), 1.50 (1H, m), 1.35-1.05 (5H, m).

Preparation 70

(Z)-(2*S*)-1-[(Cyclohexylmethyl)sulfonyl]-*N*'^{2}-(formyloxy)-2-piperidinecarboximidamide

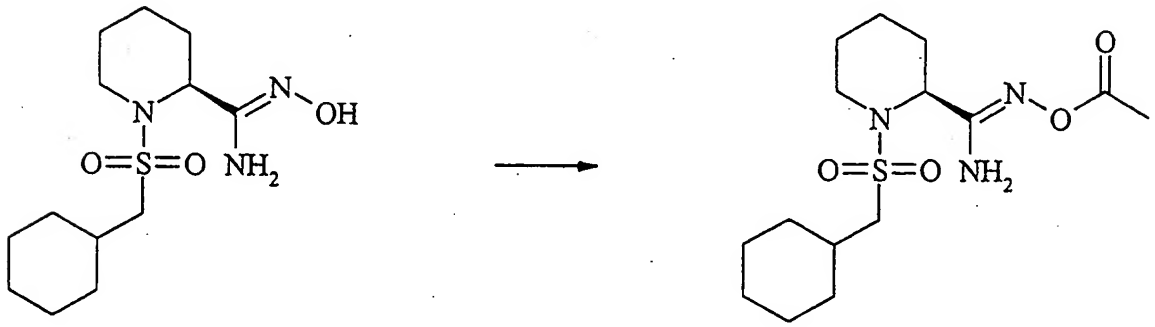


The title compound was prepared by a similar method to Preparation 5 from (Z)-(2S)-1-[cyclohexylmethylsulfonyl]-N'^{2}-hydroxy-2-piperidinecarboximidamide [see Preparation 28], formic acid, N-methyl morpholine, hydroxybenzotriazole hydrate and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, to afford (Z)-(2*S*)-1-[(cyclohexylmethyl)sulfonyl]-*N*'^{2}-(formyloxy)-2-piperidinecarboximidamide as a colourless oil.

^{1}H-NMR ($CDCl_3$) δ : 8.55 (1H, s), 5.35 (2H, bs), 4.60 (1H, d), 3.80 (1H, d), 3.10 (1H, t), 2.95 (2H, d), 2.35 (1H, d), 2.00 (3H, m), 1.80-1.40 (7H, m), 1.35-1.05 (6H, m).

Preparation 71

(Z)-(2*S*)-*N*'^{2}-(Acetyloxy)-1-[(cyclohexylmethyl)sulfonyl]-2-piperidinecarboximidamide

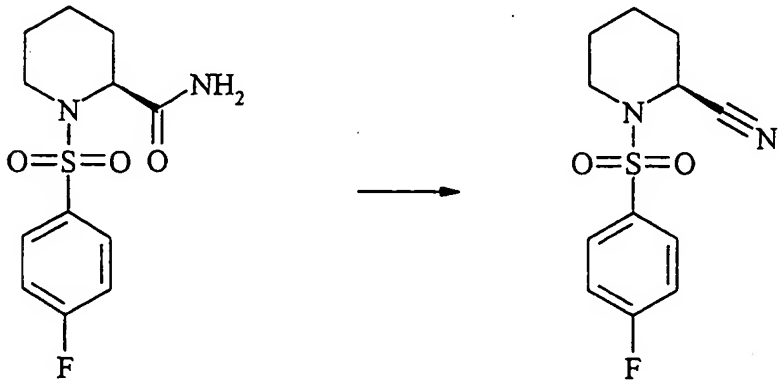


The title compound was prepared by a similar method to Preparation 5 from (Z)-(2S)-1-[cyclohexylmethylsulfonyl]-N'^{2}-hydroxy-2-piperidinecarboximidamide [see Preparation 28], acetic acid, N-methyl morpholine, hydroxybenzotriazole hydrate and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, to afford (Z)-(2*S*)-*N*'^{2}-(acetyloxy)-1-[(cyclohexylmethyl)sulfonyl]-2-piperidinecarboximidamide as a colourless oil.

^{1}H-NMR ($CDCl_3$) δ : 5.20 (2H, bs), 4.60 (1H, d), 3.80 (1H, d), 3.10 (1H, t), 2.95 (2H, d), 2.40 (1H, d), 2.20 (3H, s), 2.00 (3H, m), 1.90 (1H, m), 1.80-1.40 (7H, m), 1.35-1.05 (5H, m).

Preparation 72

(2*S*)-1-[(4-Fluoroph nyl)sulfonyl]-2-piperidylcarbonitrile



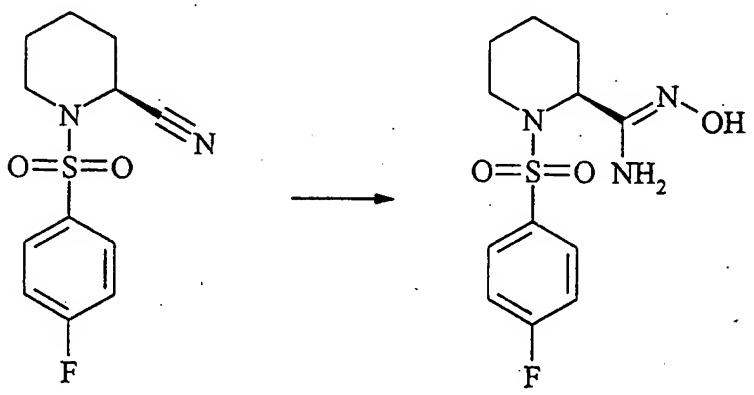
The title compound was prepared by a similar method to Preparation 3 from (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboxamide [see Preparation 40] and oxalyl chloride. The crude product was filtered through a pad of silica eluting with dichloromethane to afford (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidylcarbonitrile as an oil.

^{1}H-NMR ($CDCl_3$) δ : 7.90 (2H, m), 7.30 (2H, m), 5.00 (1H, s), 3.85 (1H, d), 2.75 (1H, t), 2.00-1.50 (6H, m).

Rotation : $[\alpha]_D^{25}$ = -111.40° (c = 0.1, methanol).

Preparation 73

(Z)-(2*S*)-1-[(4-Fluorophenyl)sulfonyl]-*N*^{1}-hydroxy-2-piperidylcarboximidamide

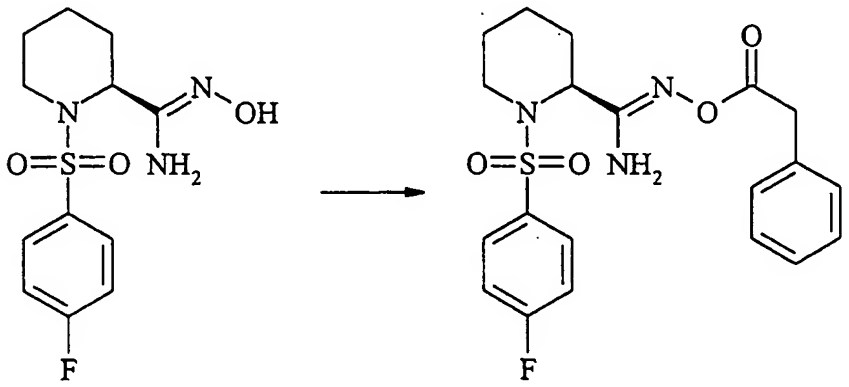


The title compound was prepared by a similar method to Preparation 4 from (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidylcarbonitrile [see Preparation 72] and hydroxylamine, to afford (Z)-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-*N*^{1}-hydroxy-2-piperidylcarboximidamide as an oil.

^{1}H-NMR ($CDCl_3$) δ : 7.90 (2H, m), 7.25 (2H, m), 6.45 (1H, bs), 5.00 (2H, bs), 4.60 (1H, d), 3.90 (1H, d), 3.10 (1H, m), 2.00 (1H, d), 1.80 (1H, m), 1.50 (2H, m), 1.20 (2H, m).

Preparation 74

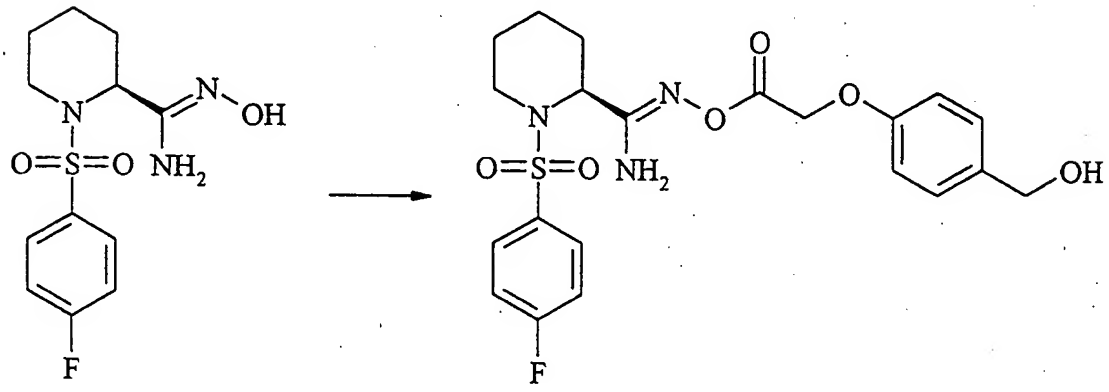
(Z)-(2*S*)-1-[(4-Fluoroph nyl)sulfonyl]-*N*'^{1}-[(2-phenylacetyl)oxy]-2-piperidylcarboximidamide



The title compound was prepared by a similar method to Preparation 53 from (Z)-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-*N*'^{1}-hydroxy-2-piperidylcarboximidamide [see Preparation 73] and phenylacetyl chloride, to afford (Z)-(2S)-1-[(4-fluorophenyl)sulfonyl]-N'^{1}-[(2-phenylacetyl)oxy]-2-piperidylcarboximidamide, which was used immediately without isolation.

Preparation 75

(Z)-(2*S*)-1-[(4-Fluorophenyl)sulfonyl]-*N*^{1}-(2-[4-(hydroxymethyl)phenoxy]acetyloxy)-2-piperidylcarboximidamide

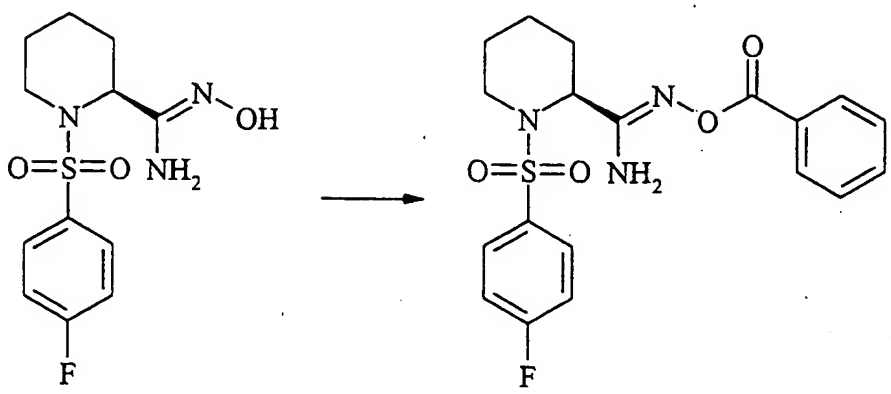


The title compound was prepared by a similar method to Preparation 5 from (Z)-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-*N*^{1}-hydroxy-2-piperidylcarboximidamide [see Preparation 73], 4-(hydroxymethyl)phenoxyacetic acid, N-methyl morpholine, hydroxybenzotriazole hydrate, and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, to afford (Z)-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-*N*^{1}-(2-[4-(hydroxymethyl)phenoxy]acetyloxy)-2-piperidylcarboximidamide as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 7.85 (2H, m), 7.25 (2H, m), 6.85 (2H, m), 6.80 (2H,m), 5.15 (3H, m), 4.80 (2H, s), 4.60 (2H, m), 3.80 (1H, d), 3.10 (1H, t), 2.15 (1H, d), 1.80 (1H, m), 1.50 (2H, m), 1.20 (2H, m).

Preparation 76

(Z)-(2*S*)-*N*'^{1}-(Benzoyloxy)-1-[(4-fluorophenyl)sulfonyl]-2-piperidylcarboximidamide

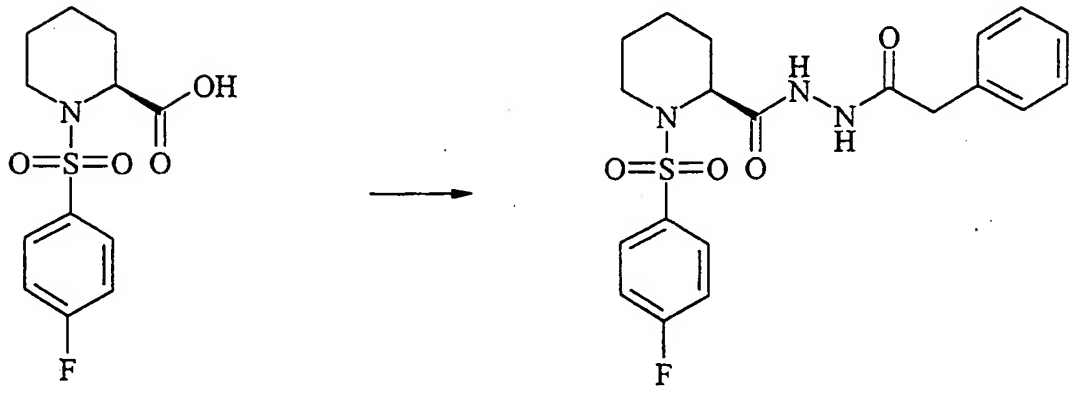


The title compound was prepared by a similar method to Preparation 5 from (Z)-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-*N*'^{1}-hydroxy-2-piperidylcarboximidamide [see Preparation 73], benzoic acid, N-methyl morpholine, hydroxybenzotriazole hydrate and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, to afford (Z)-(2S)-N'^{1}-(benzoyloxy)-1-[(4-fluorophenyl)sulfonyl]-2-piperidylcarboximidamide as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 8.05 (2H, d), 7.90 (2H, t), 7.60 (1H, m), 7.45 (2H, m), 7.25 (2H, m), 5.25 (2H, m), 4.60 (1H, d), 3.85 (1H, d), 3.20 (1H, t), 2.30 (1H, d), 1.90 (1H, m), 1.50 (2H, m), 1.20 (2H, m).

Preparation 77

(2*S*)-1-[(4-Fluorophenyl)sulfonyl]-*N*^{1}-(2-phenylacetyl)-2-piperidylcarbohydrazide

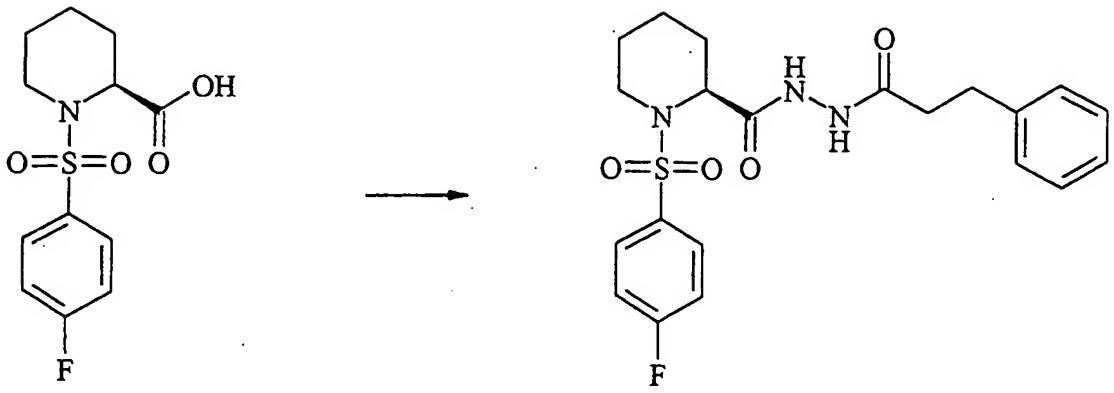


The title compound was prepared by a similar method to Preparation 39 from (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboxylic acid [see Preparation 38], phenylacetic acid hydrazide, N-methyl morpholine, hydroxybenzotriazole hydrate and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, to afford (2*S*)-1-[(4-fluorophenyl)sulfonyl]-*N*^{1}-(2-phenylacetyl)-2-piperidylcarbohydrazide as a white foam.

^{1}H-NMR ($CDCl_3$) δ : 7.90 (2H, m), 7.70 (1H, bs), 7.40-7.20 (7H, m), 4.60 (1H, d), 3.90 (1H, d), 3.65 (2H, s), 3.40 (1H, t), 2.20 (1H, d), 1.60-1.40 (3H, m), 1.30-1.10 (2H, m).

Preparation 78

(2*S*)-1-[(4-Fluorophenyl)sulfonyl]-*N*'-(3-phenylpropanoyl)-2-piperidylcarbohydrazide

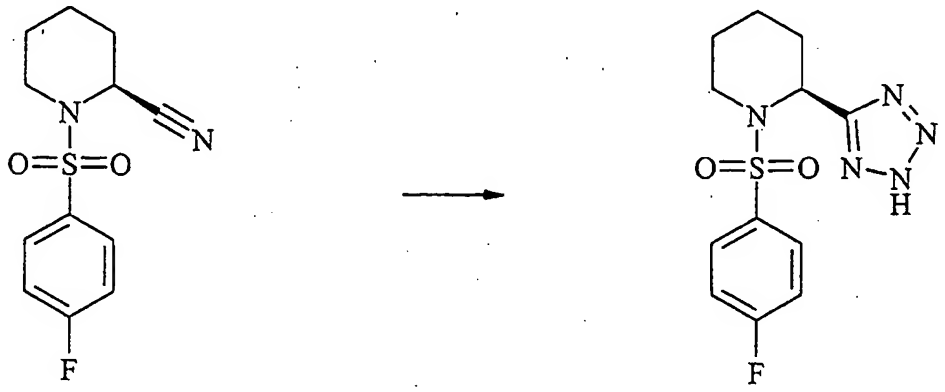


The title compound was prepared by a similar method to Preparation 39 from (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboxylic acid [see Preparation 38], 3-phenylpropanohydrazide, N-methyl morpholine, hydroxybenzotriazole hydrate and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, to afford (2S)-1-[(4-fluorophenyl)sulfonyl]-N'[1]-(3-phenylpropanoyl)-2-piperidylcarbohydrazide as a colourless gum.

^{1}H-NMR ($CDCl_3$) δ : 8.60 (1H, bs), 7.95 (2H, m), 7.65 (1H, bs), 7.40-7.20 (7H, m), 4.65 (1H, s), 3.95 (1H, d), 3.40 (1H, t), 3.00 (2H, t), 2.60 (2H, t), 2.25 (1H,d), 1.60-1.40 (3H, m), 1.30-1.15 (2H, m).

Preparation 79

(2*S*)-1-[(4-Fluorophenyl)sulfonyl]-2-(2*H*-1,2,3,4-tetraazol-5-yl)piperidine



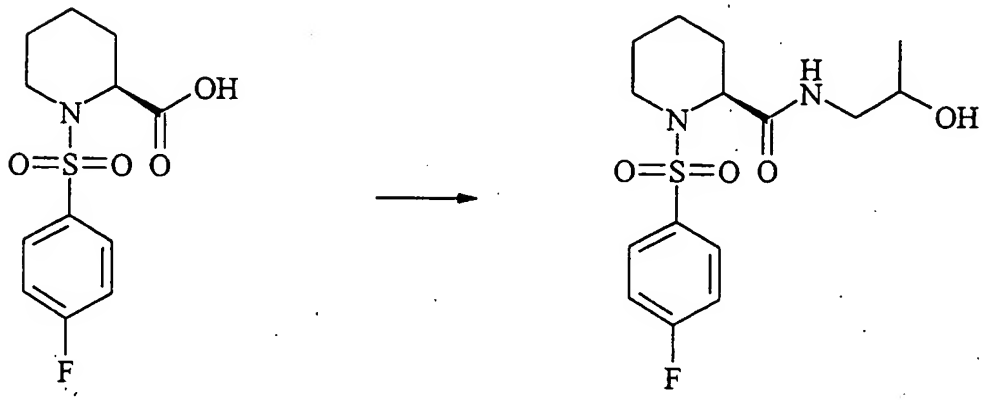
Trimethylsilyl azide (0.66ml) and dibutyltin oxide (62mg) were added to a solution of (2*S*)-1-[(4-Fluorophenyl)sulfonyl]-2-piperidylcarbonitrile (670mg) [see Preparation 72] in toluene (10ml). The reaction mixture was heated to reflux and stirred for 18hrs, after which time the cooled reaction mixture was purified by coloumn chromatography on silica gel eluting with a solvent gradient of 100 : 0 changing to 98 :2, by volume, dichloromethane : methanol followed by 98:1.98:0.02 changing to 95:4.95:0.05, by volume, dichloromethane : methanol : acetic acid. The fractions containing the product were evaporated under reduced pressure and the residue partitioned between diethyl ether and saturated sodium bicarbonate solution. The aqueous layer was separated and acidified with conc. aqueous hydrochloric acid and the product extracted with dichloromethane, dried over magnesium sulphate and the solvent removed under reduced pressure to afford (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-(2*H*-1,2,3,4-tetraazol-5-yl)piperidine (735mg) as a white foam.

^{1}H-NMR ($CDCl_3$) δ : 7.90 (2H, m), 7.25 (2H, m), 5.20 (1H, s), 3.80 (1H, d), 2.95 (1H, t), 2.55 (1H, d), 1.80-1.60 (4H, m), 1.40 (1H, m).

Rotation : $[\alpha]_D^{25}$ = -43.46° (c = 0.1, methanol).

Preparation 80

(2*S*)-1-[(4-Fluorophenyl)sulfonyl]-*N*²-(2-hydroxypropyl)-2-piperidinecarboxamide

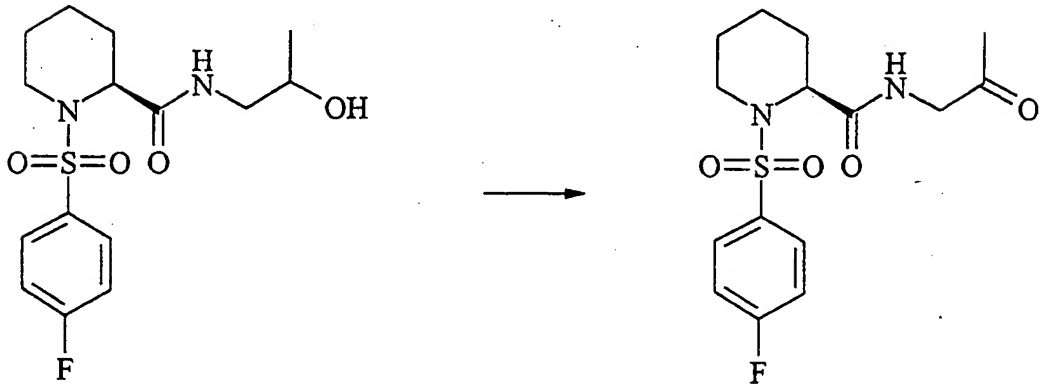


Hydroxybenzotriazole hydrate (297mg), (3-dimethylminopropyl)-3-ethyl carbodiimide (421mg) and N-methylmorpholine (241ml) were added to a solution of (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboxylic acid (575mg) [see Preparation 38]. The reaction mixture was stirred for 15mins, then 2-aminopropanol (170ml) was added and stirring continued for 18hrs at room temperature. The mixture was then diluted with ethyl acetate and washed with 2M aqueous hydrochloric acid, saturated sodium hydrogen carbonate and water. The organic layer was separated, dried over magnesium sulphate and the solvent removed under reduced pressure to afford (2*S*)-1-[(4-fluorophenyl)sulfonyl]-*N*²-(2-hydroxypropyl)-2-piperidinecarboxamide (555mg) as an oil.

^{1}H-NMR ($CDCl_3$) δ : 7.90 (2H, m), 7.30 (2H, m), 6.95 (1H, bs), 4.55 (1H, m), 3.90 (2H, m), 3.50 (1H, m), 3.20 (2H, m), 2.30 (1H, d), 1.50 (3H, m), 1.20 (5H, s).

Preparation 81

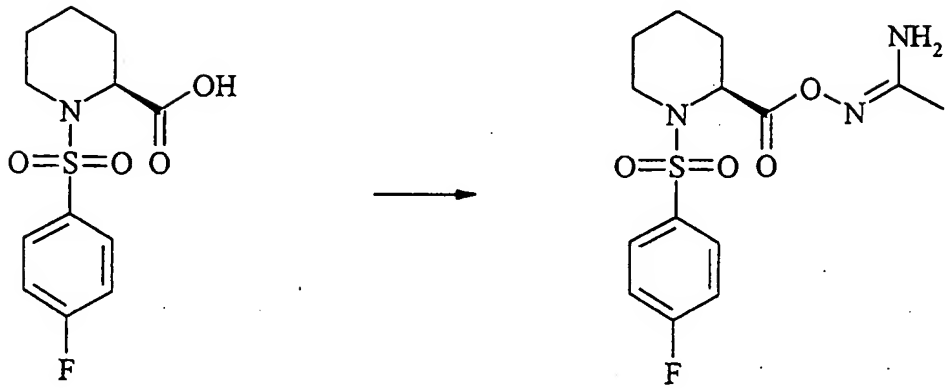
(2*S*)-1-[(4-Fluorophenyl)sulfonyl]-*N*^{2}-(2-oxopropyl)-2-piperidinecarboxamide



Dess-Martin reagent (814mg) was added to a stirred solution of (2*S*)-1-[(4-fluorophenyl)sulfonyl]-*N*^{2}-(2-hydroxypropyl)-2-piperidinecarboxamide (548mg) [see Preparation 80] and triethylamine (0.89ml) in dichloromethane (20ml). The reaction mixture was stirred for 1hr after which time the mixture was filtered through a pad of basic alumina and washed through with dichloromethane to afford (2*S*)-1-[(4-fluorophenyl)sulfonyl]-*N*^{2}-(2-oxopropyl)-2-piperidinecarboxamide (300mg).

Preparation 82

N'^1-[((2*S*)-1-[(4-Fluoroph nyl)sulfonyl]-2-piperidylcarbonyl)oxy]ethanimidamide

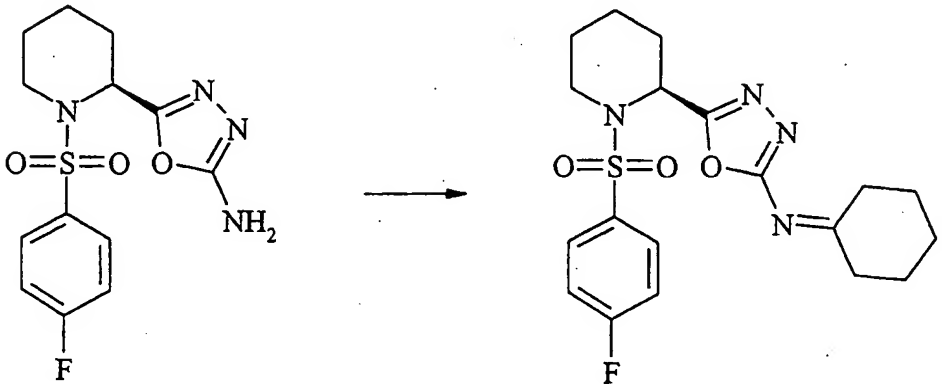


The title compound was prepared by a similar method to Preparation 39 from (2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidinecarboxylic acid [see Preparation 38], N'^1-hydroxyethanimidamide [La Manna, et al, Theochem (1990), 69, 161-68], N-methyl morpholine, hydroxybenzotriazole hydrate and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, to afford N'^1-[((2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidylcarbonyl)oxy]ethanimidamide as a colourless gum.

^{1}H-NMR ($CDCl_3$) δ : 7.90 (2H, m), 7.20 (2H, t), 4.90 (1H, bs), 3.50 (1H, d), 3.20 (1H, t), 2.00 (3H, s), 1.70 (4H, m), 1.50 (1H, m), 1.30 (1H, m).

Preparation 83

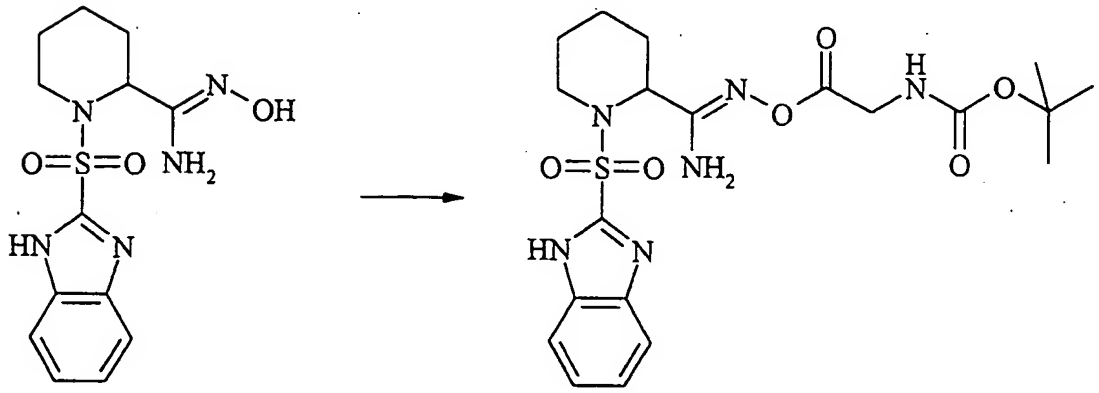
N^2-Cyclohexyliden-5-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidyl-1,3,4-oxadiazol-2-amine



Tosic acid (2.0mg) was added to a solution of 5-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-2-piperidyl-1,3,4-oxadiazol-2-amine (245mg) [see Example 32] and cyclohexanone (155ml) in toluene (20ml). The reaction mixture was fitted with a dean-stark tube and heated to reflux for 22hrs, after which time the mixture was evaporated under reduced pressure to a low volume and used immediately for Example 48.

Preparation 84

tert-Butyl *N*-2-[((*Z*)-amino[1-(1*H*-benzo[d]imidazol-2-ylsulfonyl)-2-piperidyl]methylideneamino)oxy]-2-oxoethylcarbamate

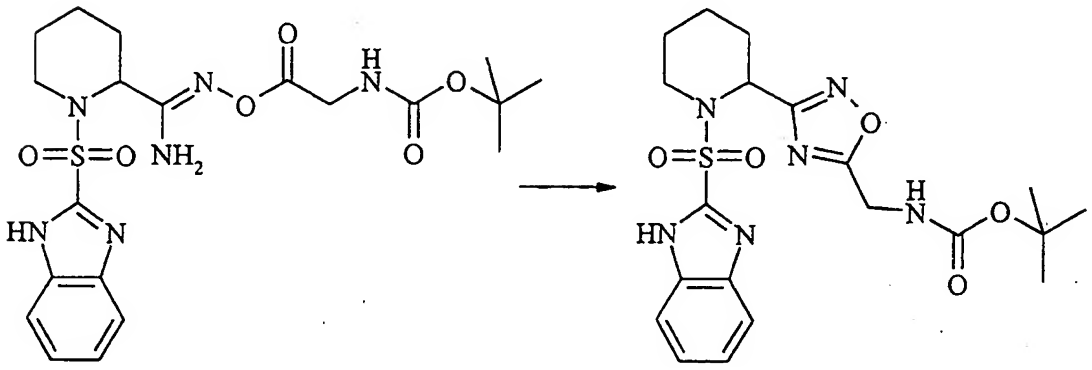


The subtitle compound was prepared by a similar method to Preparation 5 from (Z)-1-(1H-benzo[d]imidazol-2-ylsulfonyl)-N'²-hydroxy-2-piperidinecarboximidamide [see Preparation 19], 4-(hydroxymethyl)phenoxyacetic acid, N-methyl morpholine, hydroxybenzotriazole hydrate and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, to afford, *tert*-butyl *N*-2-[((*Z*)-amino[1-(1*H*-benzo[d]imidazol-2-ylsulfonyl)-2-piperidyl]methylideneamino)oxy]-2-oxoethylcarbamate as an oil.

^{1}H-NMR ($CDCl_3$) δ : 7.70 (2H, d), 7.35 (2H, m), 6.80 (2H, bs), 4.90 (1H, s), 3.85 (2H, d), 3.70 (1H, m), 3.35 (1H, t), 2.10 (1H, m), 1.60 (4H, m), 1.40 (9H, s), 1.25 (1H,m).

Preparation 85

tert-Butyl *N*-(3-[1-(1*H*-benzo[d]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethyl)carbamate

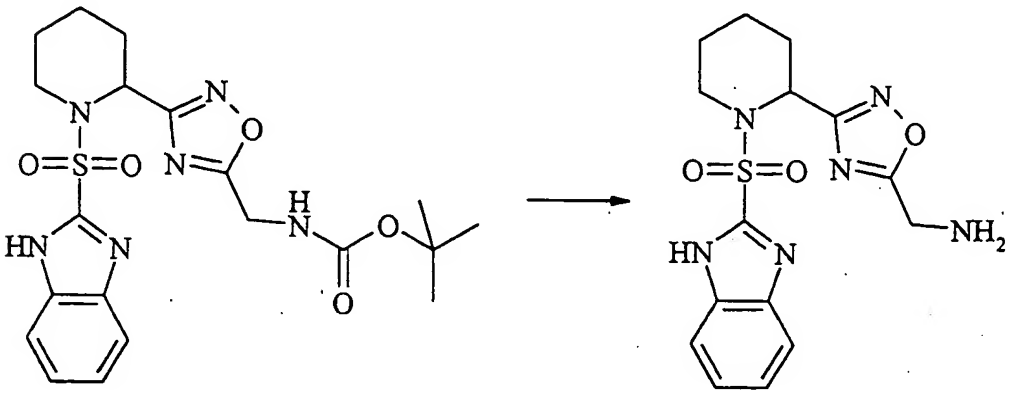


The title compound was prepared by the method of Example 16 from *tert*-butyl *N*-2-[((*Z*)-amino[1-(1*H*-benzo[d]imidazol-2-ylsulfonyl)-2-piperidyl]methylideneamino)oxy]-2-oxoethylcarbamate [see Preparation 84] and pyridine. The crude product was purified by column chromatography on silica gel eluting with 70:30, by volume, hexane : ethyl acetate, to afford *tert*-butyl *N*-(3-[1-(1*H*-benzo[d]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethyl)carbamate as an oil.

^{1}H-NMR (d6-DMSO) δ : 13.65 (1H, bs), 7.80 (1H, d), 7.60 (2H, m), 7.40-7.30 (2H, m), 5.40 (1H, d), 4.20 (2H, d), 3.95 (1H, d), 3.40 (1H, m), 2.00 (1H, m), 1.80 (1H, m), 1.60-1.50 (2H, m), 1.40 (9H, s), 1.30-1.20 (2H, m).

Preparation 86

3-[1-(1*H*-Benzo[d]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethylamine

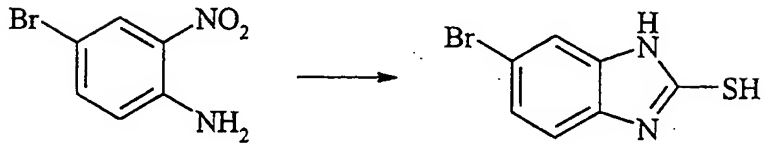


tert-Butyl *N*-(3-[1-(1*H*-benzo[d]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethyl)carbamate (0.88g) [see Preparation 85] was dissolved in dioxan (20ml) and cooled to 0°C. Hydrogen chloride gas was then bubbled through for 10mins. The reaction mixture was then stirred at room temperature for 1hr, the solvent was then removed under reduced pressure to afford 3-[1-(1*H*-benzo[d]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethylamine (0.67g) as the hydrochloride salt as a white solid.

^{1}H-NMR (d6-DMSO) δ : 9.00 (3H, bs), 7.70 (2H, d), 7.40 (2H, m), 5.45 (1H, m), 4.40 (2H, s), 3.90 (1H, d), 3.40 (1H, t), 2.05 (1H, bs), 1.80 (1H, m), 1.55 (2H, m), 1.40-1.15 (2H, m).

Preparation 87

5-Bromo-1*H*-benzo[d]imidazole-2-thiol



Platinum dioxide (5.7g) was hydrogenated in ethanol (300ml) at 50psi for 30 mins, 4-bromo-2-nitroaniline (15.0g) was then added and the solution was hydrogenated at 50psi for a further 3hrs. The mixture was then filtered through a plug of Arbocel and the ethanolic solution added to a solution of potassium hydroxide (5.8g) and carbon disulphide (17.51ml) in water (50ml). The reaction mixture was then refluxed at 85°C for 2hrs, after which time the cooled reaction mixture was diluted with water and acidified with 2M aqueous hydrochloric acid. A green solid formed which was filtered off and washed with water. The solid was dissolved in ethyl acetate and washed with 2M aqueous hydrochloric acid, dried over magnesium sulphate and the solvent was removed under reduced pressure to afford crude product. The filtration mother liquors were then extracted with ethyl acetate, the organic layer was washed with 2M aqueous hydrochloric acid, dried over magnesium sulphate and the solvent was removed under reduced pressure to afford further crude product. The combined crude products were purified by column chromatography on silica gel eluting with a solvent gradient of 70:30 changing to 0:100, by volume, hexane : ethyl acetate, in 10% increments, to afford 5-bromo-1*H*-benzo[d]imidazole-2-thiol (5.64g) as a white solid.

^{1}H-NMR (d6-DMSO) δ : 7.25 (2H, d), 7.05 (1H, d).

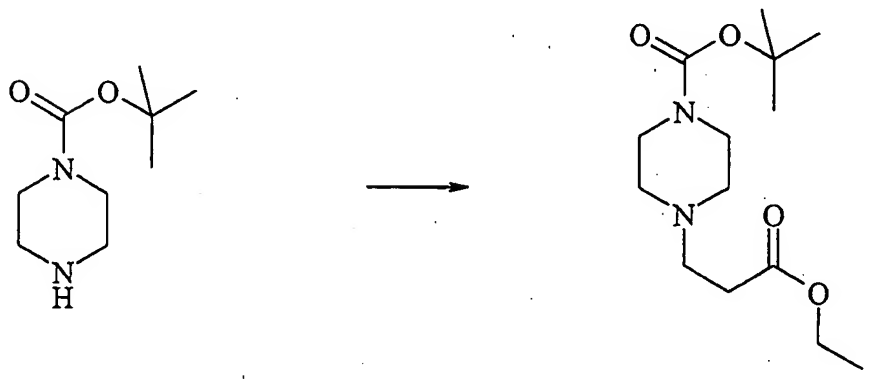
Preparation 88

5-Bromo-1*H*-benzo[d]imidazole-2-sulfonyl chloride

Chlorine gas was bubbled through a solution of 5-bromo-1*H*-benzo[d]imidazole-2-thiol (4.98g) [see Preparation 87] in 20% glacial acetic acid (100ml) at 0°C for 8mins. The precipitate formed was quickly filtered and the solid washed with ice cold water to afford 5-bromo-1*H*-benzo[d]imidazole-2-sulfonyl chloride as a solid which was used immediately for Examples 54 and 55.

Preparation 89

tert-Butyl 4-(3-ethoxy-3-oxopropyl)-1-piperazinecarboxylate

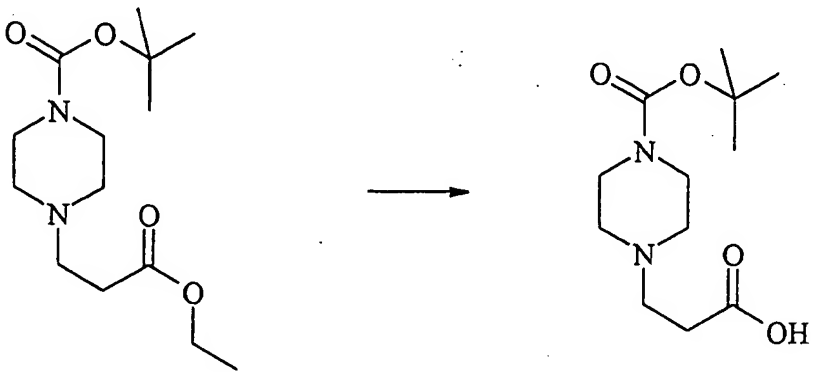


Ethyl-3-bromoproprionate (1.67ml) was added to a suspension of *tert*-butyl-1-piperazine carboxylate (2.43g) and potassium carbonate (2.16g) in acetonitrile (30ml). The reaction mixture was stirred for 56hrs at room temperature, after which time the solvent was removed under reduced pressure and the residue partitioned between dichloromethane and water. The organic layer was separated, dried over magnesium sulphate and the solvent removed under reduced pressure to afford *tert*-butyl 4-(3-ethoxy-3-oxopropyl)-1-piperazinecarboxylate (2.44g) as an oil.

^{1}H-NMR ($CDCl_3$) δ : 4.20 (2H, q), 3.40 (4H, m), 2.70 (2H, t), 2.50 (2H, t), 2.40 (4H, m), 1.45 (9H, s), 1.25 (3H, t).

Preparation 90

3-[4-(*tert*-Butoxycarbonyl)piperazino]propanoic acid

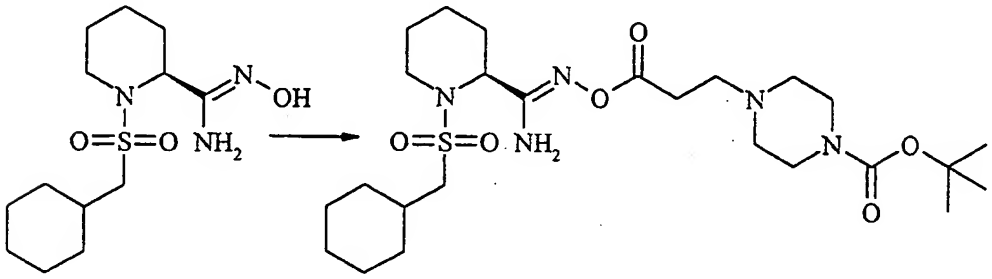


1N Aqueous lithium hydroxide (15.6ml) was added to a solution of *tert*-butyl 4-(3-ethoxy-3-oxopropyl)-1-piperazinecarboxylate (2.23g) [see Preparation 89] in ethanol (95ml). The reaction mixture was stirred for 18hrs at room temperature, after which time the solvent was removed under reduced pressure. The crude product was purified by column chromatography on reverse phase MCI gel eluting with 1:1, acetonitrile : water and further purified on Dowex 50W-X8-100 ion-exchange resin eluting with water and then 10% ammonia to afford 3-[4-(*tert*-butoxycarbonyl)piperazino]propanoic acid (1.33g) as a white solid.

^{1}H-NMR (d4-CH_3OH) δ : 3.55 (2H, m), 3.20 (2H, m), 2.80 (4H, m), 2.50-2.40 (4H, m), 1.45 (9H, s).

Preparation 91

tert-Butyl 4-(3-[((*Z*)-amino(2*S*)-1-[(cyclohexylmethyl)sulfonyl]-2-piperidylmethylidene)amino]oxy-3-oxopropyl)-1-piperazinecarboxylate

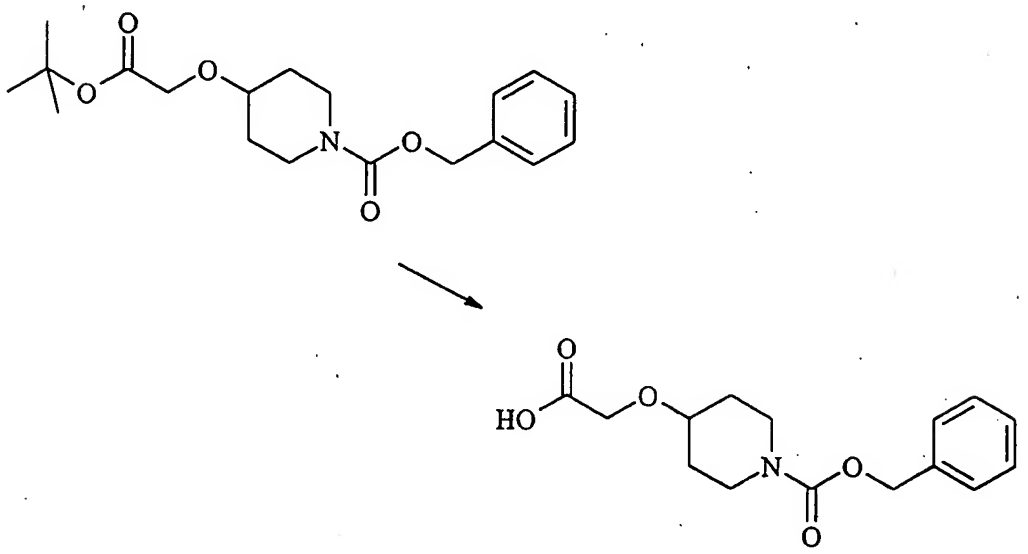


The title compound was prepared by a similar method to Preparation 5 from (Z)-(2S)-1-[cyclohexylmethylsulfonyl]-N'^{2}-hydroxy-2-piperidinecarboximidamide [see Preparation 28] and 3-[4-(*tert*-butoxycarbonyl)piperazino]propanoic acid [see Preparation 90] to afford *tert*-butyl 4-(3-[((*Z*)-amino(2*S*)-1-[(cyclohexylmethyl)sulfonyl]-2-piperidylmethylidene)amino]oxy-3-oxopropyl)-1-piperazinecarboxylate as a brown oil.

^{1}H-NMR ($CDCl_3$) δ : 5.50 (2H, bs), 4.60 (1H, d), 3.80 (1H, d), 3.45 (6H, m), 3.15 (1H, t), 2.95 (2H, m), 2.75 (3H, m), 2.65 (2H, m), 2.50 (6H, m), 2.00 (4H, m), 1.80-1.60 (4H, m), 1.50 (9H, s), 1.35 (2H, m), 1.20 (2H, m).

Preparation 92

2-(1-[(B nzyloxy)carbonyl]-4-piperidyloxy)acetic acid

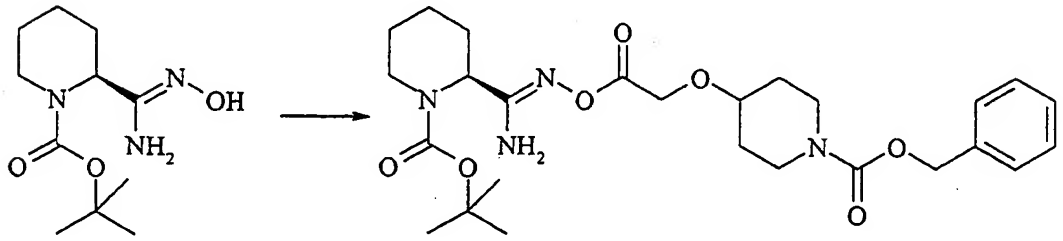


Trifluoroacetic acid (25ml) was added to a solution of benzyl 4-[2-(*tert*-butoxy)-2-oxoethoxy]-1-piperidinecarboxylate (5.90g) [J. Med. Chem, (1992), 35(23), 4405] in dichloromethane (50ml) at 0°C. The reaction mixture was then stirred at room temperature for 2hrs, after which time the solvent was removed under reduced pressure and the residue partitioned between water and ethyl acetate. The organic layer was separated and washed with 2N aqueous hydrochloric acid, brine, dried over magnesium sulphate and the solvent was removed under reduced pressure to afford 2-(1-[(benzyloxy)carbonyl]-4-piperidyloxy)acetic acid (5.13g) as a clear oil.

^{1}H-NMR ($CDCl_3$) δ : 9.45 (1H, bs), 7.20 (5H, m), 5.20 (2H, s), 4.20 (2H, s), 3.85 (2H, m), 3.65 (1H, m), 3.30 (2H, m), 1.90 (2H, m), 1.65 (2H, m).

Preparation 93

tert-Butyl (Z)-(2*S*)-2-[amino([2-(1-[(benzyloxy)carbonyl]-4-piperidyloxy)acetyl]oxyimino)methyl]-1-piperidinecarboxylate

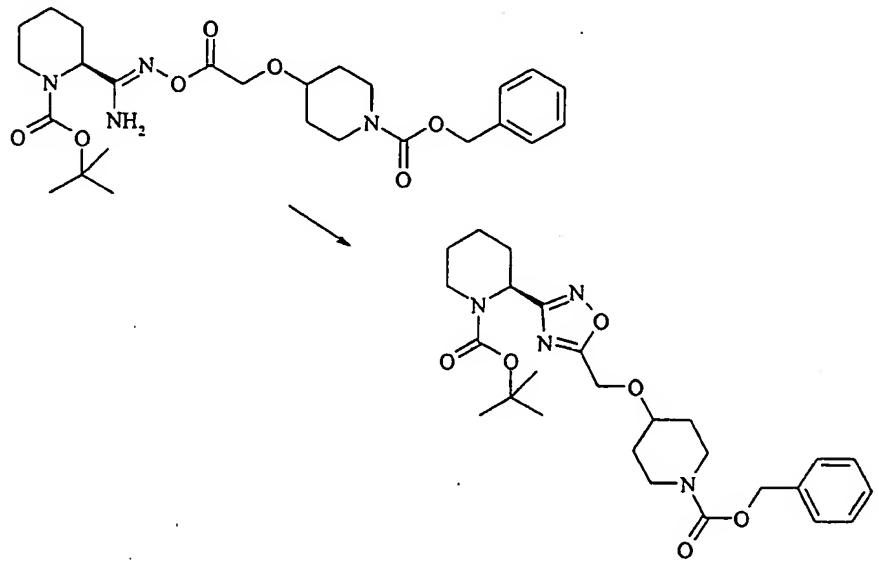


The title compound was prepared by a similar method to Preparation 5 from *tert*-butyl (Z)-(2*S*)-2-[amino(hydroxyimino)methyl]-1-piperidinecarboxylate [see Preparation 4] and 2-(1-[(benzyloxy)carbonyl]-4-piperidyloxy)acetic acid [see Preparation 92] to afford *tert*-butyl (Z)-(2*S*)-2-[amino([2-(1-[(benzyloxy)carbonyl]-4 piperidyloxy)acetyl]oxyimino) methyl]-1-piperidinecarboxylate as a brown oil.

^{1}H-NMR ($CDCl_3$) δ : 7.40 (5H, m), 5.15 (2H, s), 5.05 (2H, bs), 4.95 (1H, d), 4.35 (2H, s), 4.05 (1H, d), 3.80 (2H, m), 3.65 (1H, m), 3.25 (2H, m), 2.80 (1H, t), 2.25 (1H, d), 1.90-1.60 (8H, m), 1.55 (9H, m), 1.40 (1H,m).

Preparation 94

tert-Butyl (2*S*)-2-{5-[(1-[(benzyloxy)carbonyl]-4-piperidyloxy)methyl]-1,2,4-oxadiazol-3-yl}-1-piperidinecarboxylate

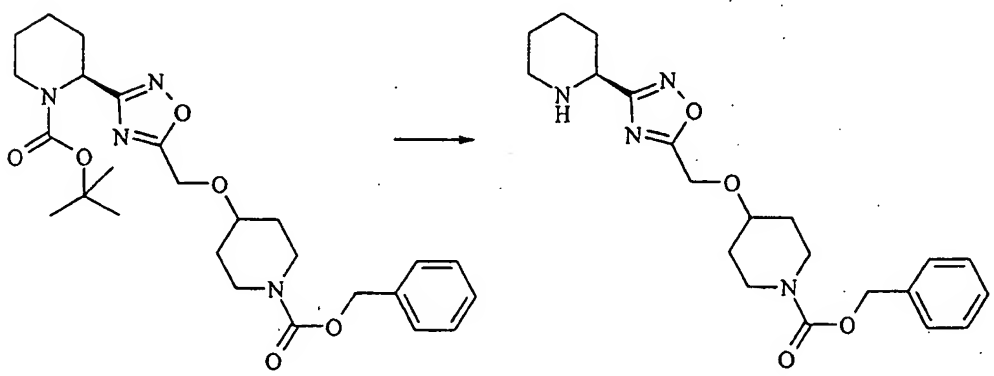


The title compound was prepared by a similar method to Preparation 13 from (Z)-(2*S*)-2-[amino([2-(1-[(benzyloxy)carbonyl]-4 piperidyloxy)acetyl]oxyimino) methyl]-1-piperidinecarboxylate [see Preparation 93] and pyridine. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 80 : 20, changing to 50 :50, by volume, hexane : ethyl acetate, in 5% increments, to afford *tert*-butyl (2*S*)-2-{5-[(1-[(benzyloxy)carbonyl]-4-piperidyloxy)methyl]-1,2,4-oxadiazol-3-yl}-1-piperidinecarboxylate.

^{1}H-NMR ($CDCl_3$) δ : 7.40 (5H, m), 5.50 (1H, bs), 5.15 (2H, s), 4.75 (2H, s), 4.10 (1H, m), 3.80 (2H, m), 3.50 (1H, m), 3.30 (2H, m), 3.00 (1H, t), 2.25 (1H, d), 1.90 (3H, m), 1.65 (5H, m), 1.45 (9H, s), 1.40 (1H,m).

Preparation 95

Benzyl 4-(3-[(2*S*)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)-1-piperidinecarboxylate

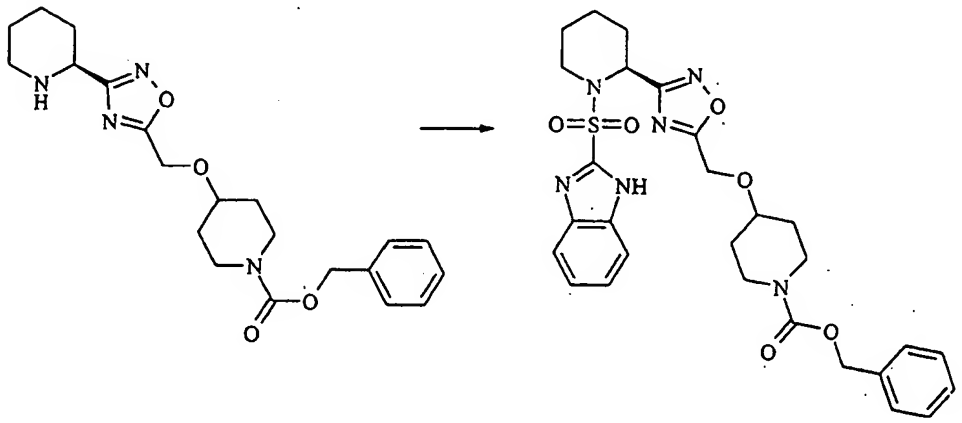


Trifluoroacetic acid (25ml) was added to a solution of *tert*-butyl (2*S*)-2-{5-[(1-[(benzyloxy)carbonyl]-4-piperidyloxy)methyl]-1,2,4-oxadiazol-3-yl}-1-piperidinecarboxylate (1.73g) [see Preparation 94] in dichloromethane (25ml) at 0°C. The reaction mixture was stirred for 2hrs at room temperature, after which time the solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The organic layer was separated and washed with 2N aqueous hydrochloric acid and brine, the combined aqueous layers were then neutralised with saturated sodium hydrogen carbonate and the product re-extracted with ethyl acetate. The organic layer was then separated, dried over magnesium sulphate and the solvent removed under reduced pressure to afford benzyl 4-(3-[(2*S*)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)-1-piperidinecarboxylate (1.33g) as a brown oil.

^{1}H-NMR ($CDCl_3$) δ : 7.40 (5H, m), 5.15 (2H, s), 4.75 (2H, s), 4.00 (1H, d), 3.80 (2H, m), 3.70 (1H, m), 3.30-3.15 (3H, m), 2.80 (1H, t), 2.10 (1H, m), 1.90 (3H, m), 1.80-1.55 (6H, m).

Preparation 96

Benzyl 4-(3-[(2*S*)-1-(1*H*-benzo[d]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)-1-piperidinecarboxylate

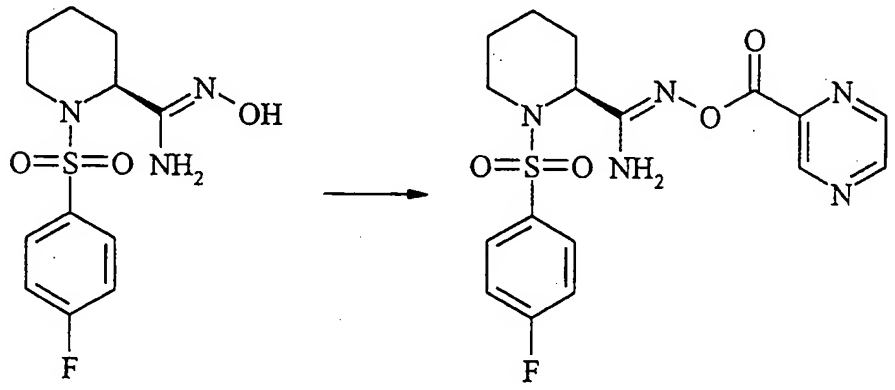


The title compound was prepared by a similar method to Example 1 from benzyl 4-(3-[(2*S*)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)-1-piperidinecarboxylate [see Preparation 95] and 1*H*-benzo[*d*]imidazol-2-sulfonyl chloride [see Preparation 8]. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of 80 : 20 changing to 0 :100, by volume, hexane : ethyl acetate, in 5% increments, to afford benzyl 4-(3-[(2*S*)-1-(1*H*-benzo[d]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)-1-piperidinecarboxylate as a clear oil.

^{1}H-NMR ($CDCl_3$) δ : 10.65 (1H, bs), 7.85 (1H, d), 7.60 (1H, d), 7.40 (7H, m), 5.60 (1H, d), 5.15 (2H, s), 4.40 (2H, s), 4.00 (1H, d), 3.80 (2H, m), 3.55 (1H, m), 3.20 (3H, m), 2.30 (1H, d), 2.05 (1H,m) 1.85-1.50 (8H, m).

Preparation 97

(Z)-(2*S*)-1-[(4-Fluorophenyl)sulfonyl]-*N*^{2}-[(2-pyrazinylcarbonyl)oxy]-2-piperidinecarboximidamide

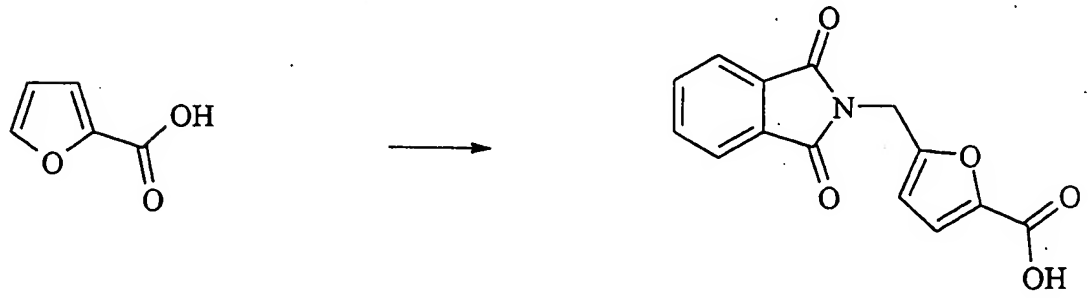


The title compound was prepared by a similar method to Preparation 5 from (Z)-(1*S*)-2-[(4-fluorophenyl)sulfonyl]-*N*^{1}-hydroxy-2-piperidylcarboximidamide [see Preparation 73], 2-pyrazinecarboxylic acid, N-methyl morpholine, hydroxybenzotriazole hydrate, dimethylaminopyridine and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, to afford (Z)-(2*S*)-1-[(4-fluorophenyl)sulfonyl]-*N*^{2}-[(2-pyrazinylcarbonyl)oxy]-2-piperidinecarboximidamide as a white solid.

^{1}H-NMR ($CDCl_3$) δ : 9.40 (1H, s), 8.80 (1H, s), 8.75 (1H, s), 7.95 (2H, m), 7.25 (2H, m), 5.50 (2H, bs), 4.70 (1H, m), 3.90 (1H, d), 3.20 (1H, t), 2.30 (1H, d), 1.90 (1H, m), 1.55 (2H, m), 1.20 (2H, m).

Preparation 98

5-[(1,3-Dioxo-2,3-dihydro-1*H*-2-isoindolyl)methyl]-2-furoic acid

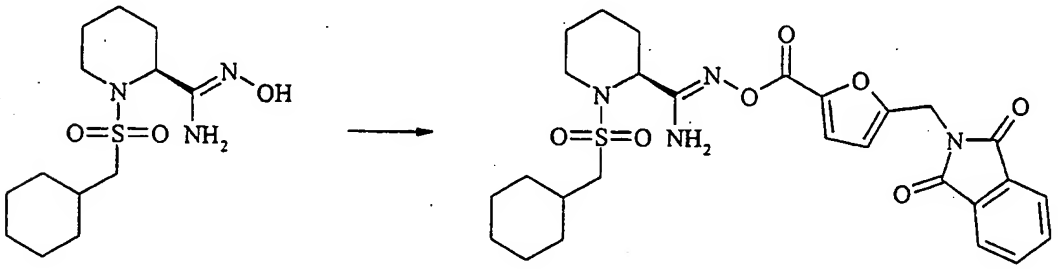


2-Furoic acid (10.0g) was dissolved in cold concentrated sulphuric acid (50ml). The mixture was then added to N-hydroxy methylphthalimide (12.0g) and the reaction mixture allowed to stand for 18hrs at room temperature. The mixture was then poured into ice and the product extracted with dichloromethane, dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was triturated with diethyl ether and recrystallised from methanol to afford 5-[(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)methyl]-2-furoic acid (9.70g) as a brown solid.

Analysis : Found C, 59.48; H, 3.72; N, 5.03; $C_{14}H_9NO_5$. 0.5 H_2O requires C, 60.00; H, 3.60; N, 5.04%.

Preparation 99

(Z)-(2*S*)-1-[(Cyclohexylmethyl)sulfonyl]-*N*'^{2}-[(5-[(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)methyl]-2-furylcarbonyl)oxy]-2-piperidinecarboximidamide

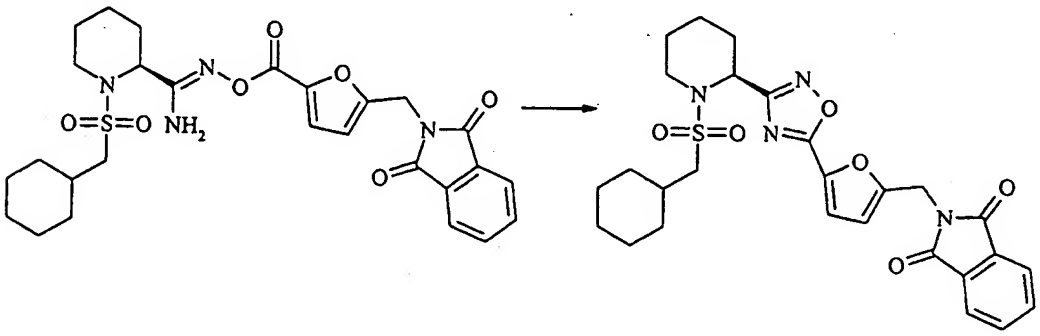


The title compound was prepared by a similar method to Preparation 5 from (Z)-(2S)-1-[(cyclohexylmethyl)sulfonyl]-N'^{2}-hydroxy-2-piperidinecarboximidamide [see Preparation 28] and 5-[(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)methyl]-2-furoic acid [see Preparation 98], to afford (Z)-(2S)-1-[(cyclohexylmethyl)sulfonyl]-N'^{2}-[(5-[(1,3-dioxo-2,3-dihydro-1H-2-isoindolyl)methyl]-2-furylcarbonyl)oxy]-2-piperidinecarboximidamide as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ : 7.90 (2H, m), 7.80 (2H, m), 7.20 (1H, s), 6.45 (1H, d), 5.30 (2H, bs), 4.95 (2H, s), 4.65 (1H, d), 3.80 (1H, d), 3.20 (1H, t), 2.95 (2H, m), 2.40 (1H, d), 2.00 (4H, m), 1.80-1.60 (7H, m), 1.50 (1H, m), 1.40-1.10 (4H, m).

Preparation 100

2-[5-(3-(2*S*)-1-[(Cyclohexylmethyl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)-2-furyl]methyl-1,3-isoindolinedione

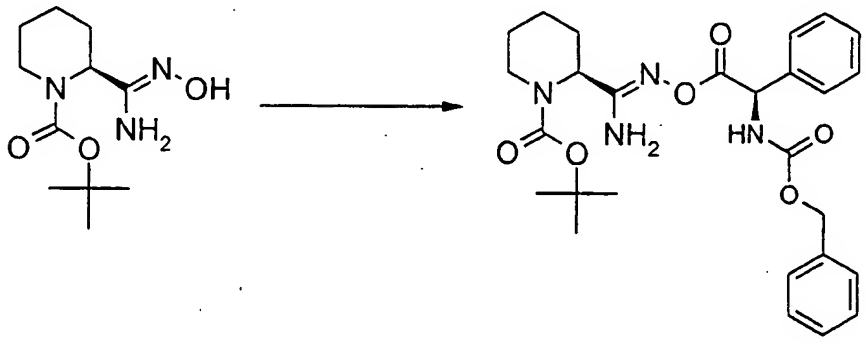


(Z)-(2S)-1-[(Cyclohexylmethyl)sulfonyl]-N'²-[(5-[(1,3-dioxo-2,3-dihydro-1H-2-isoindolyl)methyl]-2-furylcarbonyl)oxy]-2-piperidinecarboximidamide (154mg) (see Preparation 99) was dissolved in toluene (4ml) and heated to reflux for 18hrs. The toluene was removed under reduced pressure and the crude product was purified by column chromatography on silica gel eluting with 2 : 1, by volume, hexane : ethyl acetate, to afford 2-[5-(3-(2*S*)-1-[(cyclohexylmethyl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)-2-furyl]methyl-1,3-isoindolinedione (62mg) as an oil.

^{1}H-NMR ($CDCl_3$) δ : 7.90 (2H, m), 7.75 (2H, m), 7.25 (1H, d), 6.60 (1H, s), 5.40 (1H, d), 5.35 (1H, s), 5.00 (2H, s), 3.80 (1H, d), 3.25 (1H, t), 3.00 (2H, m), 2.30 (1H, d), 2.00 (4H, m) 1.80-1.60 (6H, m), 1.50 (1H, m), 1.40-1.00 (4H, m).

Preparation 101

tert-Butyl (2*S*)-2-[(*Z*,5*R*)-1-amino-4,7-dioxo-5,9-diphenyl-3,8-dioxa-2,6-diaza-1-nonen-1-yl]-1-piperidinecarboxylate

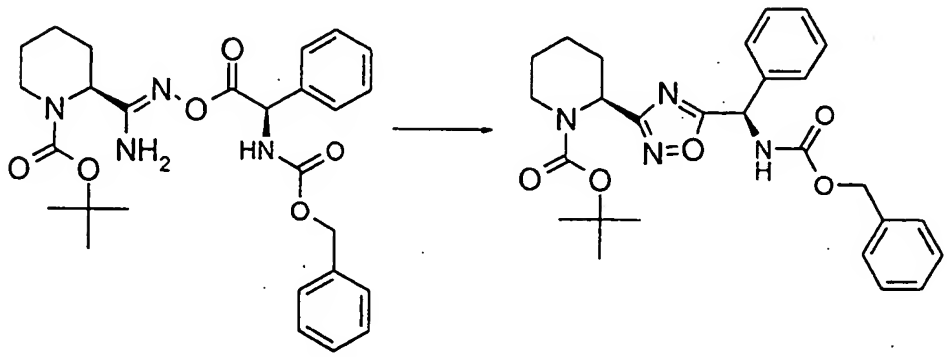


The title compound was prepared by a similar method to Preparation 5 from *tert*-butyl (*Z*)-(2*S*)-2-[amino(hydroxyimino)methyl]-1-piperidinecarboxylate [see Preparation 4] and (2*R*)-2-{[(benzyloxy)carbonyl]amino}-2-phenylethanoic acid to afford *tert*-butyl (2*S*)-2-[(*Z*,5*R*)-1-amino-4,7-dioxo-5,9-diphenyl-3,8-dioxa-2,6-diaza-1-nonen-1-yl]-1-piperidinecarboxylate as an oil.

^{1}H-NMR ($CDCl_3$) δ : 8.20 (0.5H, d), 7.35 (10H, m), 6.55 (0.5H, d), 5.90 (1H, m), 5.55 (1H, d), 5.10 (2H, m), 4.90 (2H, m), 3.95 (1H, m), 2.70 (1H, m), 2.40 (1H, m), 2.20 (1H, m), 1.80 (2H, m), 1.60 (2H, m), 1.45 (9H, s).

Preparation 102

tert-Butyl (2*S*)-2-{5-[(*R*)-{[(benzyloxy)carbonyl]amino}(phenyl)methyl]-1,2,4-oxadiazol-3-yl}-1-piperidinecarboxylate

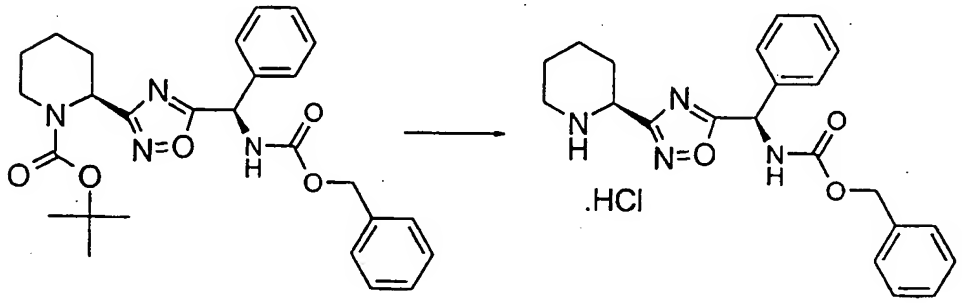


The title compound was prepared by a similar method to Preparation 6 from *tert*-butyl (2*S*)-2-[(*Z*,5*R*)-1-amino-4,7-dioxo-5,9-diphenyl-3,8-dioxa-2,6-diaza-1-nonen-1-yl]-1-piperidinecarboxylate [see Preparation 101] and pyridine to afford *tert*-butyl (2*S*)-2-{5-[(*R*)-{[(benzyloxy)carbonyl]amino}(phenyl)methyl]-1,2,4-oxadiazol-3-yl}-1-piperidinecarboxylate as an oil.

^{1}H-NMR ($CDCl_3$) δ : 7.40 (10H, m), 6.20 (1H, d), 5.85 (1H, s), 5.45 (1H, s), 5.10 (2H, m), 4.00 (1H, d), 2.95 (1H, m), 2.15 (1H, d), 1.85 (1H, m), 1.60 (2H, m), 1.45 (11H, m).

Preparation 103

Benzyl (*R*)-phenyl{3-[(2*S*)-piperidyl]-1,2,4-oxadiazol-5-yl}methylcarbamate hydrochloride

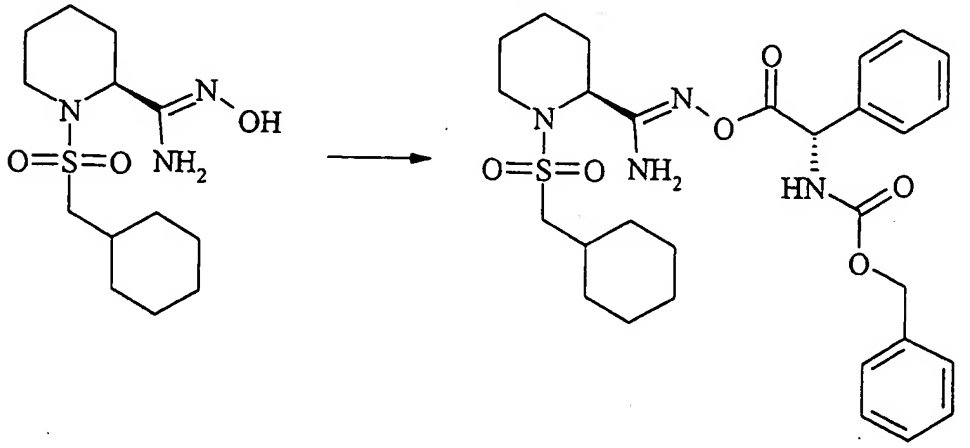


The title compound was prepared by a similar method to Preparation 7 from *tert*-butyl (2*S*)-2-{5-[(*R*)-{[(benzyloxy)carbonyl]amino}(phenyl)methyl]-1,2,4-oxadiazol-3-yl}-1-piperidinecarboxylate [see Preparation 102] and anhydrous hydrogen chloride gas to afford benzyl (*R*)-phenyl{3-[(2*S*)-piperidyl]-1,2,4-oxadiazol-5-yl}methylcarbamate hydrochloride as a foam.

^{1}H-NMR ($CDCl_3$) δ : 7.30 (10H, m), 6.25 (1H, s), 6.20 (1H, s), 5.10 (2H, s), 4.40 (1H, s), 3.55 (1H, s), 2.30 (1H, s), 1.95 (5H, m), 1.60 (1H, m).

Preparation 104

Benzyl N-[(1*S*)-2-{[((*Z*)-amino{(2*S*)-1-[(cyclohexylmethyl)sulfonyl]piperidyl}methylidene)amino]oxy}-2-oxo-1-phenylethyl]carbamate

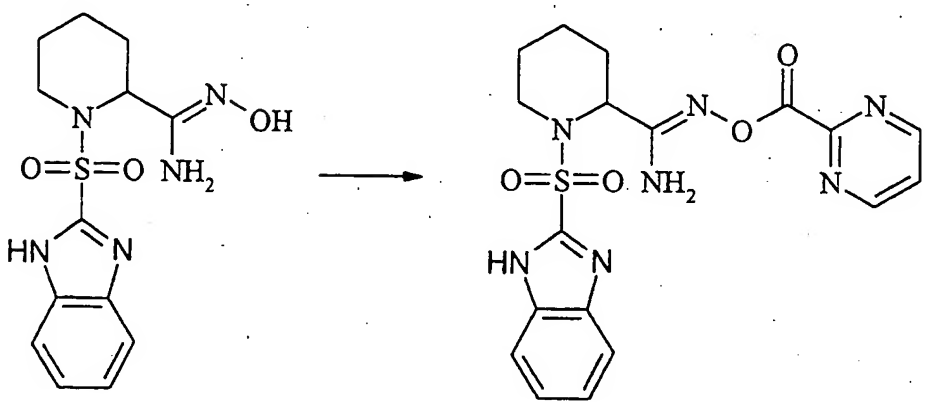


The title compound was prepared by a similar method to Preparation 5 from (Z)-(2S)-1-[cyclohexylmethylsulfonyl]-N'²-hydroxy-2-piperidinecarboximidamide [see Preparation 28] and (2*S*)-2-{[(benzyloxy)carbonyl]amino}-2-phenylethanoic acid to afford benzyl N-[(1*S*)-2-{[((*Z*)-amino{(2*S*)-1-[(cyclohexylmethyl)sulfonyl]piperidyl}methylidene)amino]oxy}-2-oxo-1-phenylethyl]carbamate as an oil.

^{1}H-NMR ($CDCl_3$) δ : 7.40 (10H, m), 5.90 (2/3H, m), 5.80 (1/3H, m), 5.55 (2/3H, m), 5.40 (1/3H, m), 5.10 (4H, m), 4.55 (1H, s), 3.70 (1H, m), 3.00 (1H, m), 2.90 (2H, m), 2.15 (1H, m), 1.95 (3H, m), 1.70 (6H, m), 1.40 (1H, m), 1.30 (3H, m), 1.05 (3H, m).

Preparation 105

1-(1*H*-Benzo[d]imidazol-2-ylsulfonyl)-N'²-[(2-pyrimidinylcarbonyl)oxy]-2-piperidinecarboximidamide



The title compound was prepared by a similar method to Preparation 20 from (Z)-1-(1H-benzo[d]imidazol-2-ylsulfonyl)-N'²-hydroxy-2-piperidinecarboximidamide [see Preparation 19] and pyrimidine-2-carboxylic acid (see Chem. Ind. (London), 1954, 786) to afford 1-(1*H*-benzo[d]imidazol-2-ylsulfonyl)-N'²-[(2-pyrimidinylcarbonyl)oxy]-2-piperidinecarboximidamide as a gum. The title compound was used directly in Example 65.

It will be appreciated that what will be claimed is as follows:

(i) a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof;

(ii) a process for the preparation of a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof;

(iii) a pharmaceutical composition comprising a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient, diluent or carrier;

(iv) a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a medicament;

(v) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of neuronal degeneration;

(vi) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the promotion of neuronal regeneration and outgrowth;

(vii) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of a neurological disease or disorder such as a neurodegenerative disease;

(viii) use as in (vii) where the neurological disease or disorder is selected from the group consisting of senile dementia (Alzheimer's disease) and other dementias, amyotrophic lateral sclerosis and other forms of motor neuron disease, Parkinson's disease, Huntington's disease, neurological deficits associated with stroke, all forms of degenerative disease affecting the central or peripheral nervous system (e.g. cerebellar-brainstem atrophies, syndromes of progressive ataxias), all forms of muscular dystrophy, progressive muscular atrophies, progressive bulbar muscular atrophy, physical or traumatic damage to the central or

peripheral nervous system (e.g. spinal cord), herniated, ruptured or prolapsed intervertebrae disc syndromes, cervical spondylosis, plexus disorders, thoracic outlet syndromes, all forms of peripheral neuropathy (both diabetic and non-diabetic), trigeminal neuralgia, glossopharyngeal neuralgia, Bell's Palsy, all forms of auto-immune related disease resulting in damage of the central or peripheral nervous system (e.g. multiple sclerosis, myasthenia gravis, Guillain-Barré syndrome), AIDS related disorders of the nervous system, dapsone ticks, bulbar and retrobulbar affections of the optic nerve (e.g. retinopathies and retrobulbar neuritis), hearing disorders such as tinnitus, and prion diseases;

(ix) use as (viii) where the neurological disease or disorder is senile dementia (Alzheimer's disease) or another dementia, amyotrophic lateral sclerosis or another form of motor neuron disease, Parkinson's disease, Huntington's disease, a neurological deficit associated with stroke, physical or traumatic damage to the central or peripheral nervous system (e.g. spinal cord), a peripheral neuropathy (either diabetic or non-diabetic), multiple sclerosis or a hearing disorder such as tinnitus;

(x) a method of treatment of a human to treat neuronal degeneration which comprises treating said human with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(xi) a method of treatment of a human to promote neuronal regeneration and outgrowth which comprises treating said human with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(xii) a method of treatment of a human to treat a neurological disease or disorder such as a neurodegenerative disease which comprises treating said human with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(xiii) a method as in (xii) where the neurological disease or disorder is selected from the group consisting of senile dementia (Alzheimer's disease) and other dementias, amyotrophic lateral sclerosis and other forms of motor neuron disease, Parkinson's disease, Huntington's disease, neurological deficits associated with stroke, all forms of degenerative disease affecting the central or peripheral nervous system (e.g. cerebellar-brainstem atrophies, syndromes of progressive ataxias), all forms of muscular dystrophy, progressive muscular atrophies, progressive bulbar muscular atrophy, physical or traumatic damage to the central or peripheral nervous system (e.g. spinal cord), herniated, ruptured or prolapsed intervertebrae disc syndromes, cervical spondylosis, plexus disorders, thoracic outlet syndromes, all forms of peripheral neuropathy (both diabetic and non-diabetic), trigeminal neuralgia, glossopharyngeal neuralgia, Bell's Palsy, all forms of auto-immune related disease resulting in damage of the central or peripheral nervous system (e.g. multiple sclerosis, myasthenia gravis, Guillain-Barré syndrome), AIDS related disorders of the nervous system, dapsone ticks, bulbar and retrobulbar affections of the optic nerve (e.g. retinopathies and retrobulbar neuritis), hearing disorders such as tinnitus, and prion diseases;

(xiv) a method as in (xiii) where the neurological disease or disorder is senile dementia (Alzheimer's disease) or another dementia, amyotrophic lateral sclerosis or another form of motor neuron disease, Parkinson's disease, Huntington's disease, a neurological deficit associated with stroke,

physical or traumatic damage to the central or peripheral nervous system (e.g. spinal cord), a peripheral neuropathy (either diabetic or non-diabetic), multiple sclerosis or a hearing disorder such as tinnitus; and

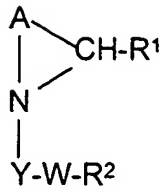
(xv) any novel intermediates described herein.

Table 6

EXAMPLE	IC_{50} (nm) FKBP-12
25	81
14	91
1	95
23	336
65	442
43	1675
42	2010
11	685 (FKBP-52, K_i)

CLAIMS

1. A compound of the formula:



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 is a 5- or 6-membered ring heteroaryl group containing either 1, 2, 3 or 4 nitrogen heteroatoms, or 1 oxygen or sulphur heteroatom and, optionally, 1 or 2 nitrogen heteroatoms, said heteroaryl group being linked to the adjacent carbon atom by a ring carbon atom and optionally substituted by from 1 to 3 substituents each independently selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, -X-(C_3-C_7 cycloalkyl), -X-aryl, -X-het, -X-OH, -X-(C_1-C_4 alkoxy), -X-CO_2R^5, -X-CN, and -X-NR^3R^4;

R^2 is H, phenyl or C_3-C_7 cycloalkyl, said phenyl or cycloalkyl being optionally benzo- or C_3-C_7 cycloalkyl-fused and optionally substituted, including in the benzo- or cycloalkyl-fused portion, by from 1 to 3 substituents each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, -OH, -(C_1-C_6 alkylene)OH, halo and halo(C_1-C_6 alkylene)-,

or R^2 is a 5-, 6- or 7-membered ring heterocyclic group containing either 1, 2, 3 or 4 nitrogen heteroatoms, or 1 oxygen or sulphur heteroatom and, optionally, 1 or 2 nitrogen heteroatoms, said heterocyclic group being saturated or partially or fully unsaturated, optionally benzo-fused and optionally substituted, including in the benzo-fused portion, by from 1 to 3 substituents each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, halo(C_1-C_6 alkylene)- and -CO_2R^5 ,

said R^2 group being attached to W by any mono- or bicyclic ring carbon atom or heteroatom; R^3 and R^4 are either each independently selected from H, C_1-C_6 alkyl,

C_3-C_6 cycloalkyl and -(C_1-C_6 alkylene)(C_3-C_6 cycloalkyl), or, when taken together, represent unbranched C_3 -C_6 alkylene optionally containing O or NR^5;

R^5 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, -(C_1-C_6 alkylene)(C_3-C_6 cycloalkyl) or -(C_1-C_6 alkylene)aryl;

A is unbranched C_3-C_5 alkylene optionally substituted by C_1-C_6 alkyl;

W is a direct link, C_1-C_6 alkylene or C_2-C_6 alkenylene;

X is a direct link, C_1-C_6 alkylene or -(C_0-C_6 alkylene)-Z-(C_0-C_6 alkylene)-;

Y is SO_2 , carbonyl, -$CONR^5$-, -CO.CO-, -CH_2CO-, -CS.CO-, -CO.CS- or -CO.CH(OH)-;

Z is O, S, -$CR^5NR^3R^4$-, -$CR^5NR^5(CO_2R^5)$-, -CR^5(aryl[1])-, -NR^5-, -NR^5CO_2 -, -$CONR^5$- or -NR^5CO-;

aryl" is phenyl optionally substituted by from 1 to 3 substituents each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, -(C_1 -C_6 alkylene)(C_1-C_6 alkoxy), halo, halo(C_1-C_6 alkylene)-, -NR^3R^4, -(C_1-C_6 alkylene)NR^3R^4, -(C_1-C_6 alkylene)OH, -O(C_1 -C_6 alkylene)NR^3R^4 and -(C_1-C_6 alkylene)(phthalimido);

"aryl[1] " is phenyl optionally substituted by from 1 to 3 substituents each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, -(C_1 -C_6 alkylene)(C_1-C_6 alkoxy), halo and halo(C_1-C_6 alkylene)-; and

"het" is a 5-, 6- or 7-membered ring heterocyclic group containing either 1, 2, 3 or 4 nitrogen heteroatoms, or 1 oxygen or sulphur heteroatom and, optionally, 1 or 2 nitrogen heteroatoms, said heterocyclic group being saturated or partially or fully unsaturated, or "het" is azetidinyl, said "het" being optionally substituted by from 1 to 3 substituents each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_7

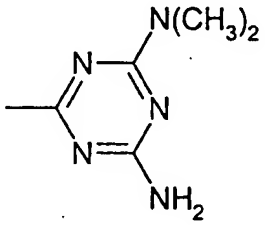
cycloalkyl, -(C_1-C_6 alkylene)(C_1-C_6 alkoxy), -(C_1-C_6 alkylene)(C_3-C_7 cycloalkyl), halo, halo(C_1-C_6 alkylene)-, -NR^3R^4, -CO_2R^5, -(C_1-C_6 alkylene)aryl and -(C_1-C_6 alkylene)NR^3R^4:

with the provisos that

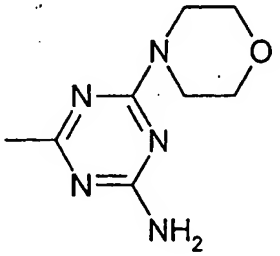
(a) the heteroaryl group of R^1 is not substituted by -(C_0-C_6 alkylene)-Z-(C_0 alkylene)(-OH or -C_1-C_4 alkoxy or -CN or -NR^3R^4) when Z is O, S, -NR^5-, -NR^5CO_2- or -$CONR^5$-;

(b) when W is a direct link, R^2 is only H when Y is -$CONR^5$- ;

(c) when A is C_3 alkylene, Y is sulphonyl, W is a direct link, and R^2 is para methyl substituted phenyl, then R^1 is not

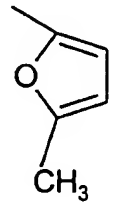


or



;

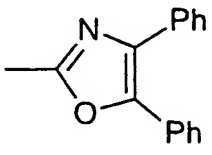
(d) when A is C_4 alkylene, Y is carbonyl, W is C_1 alkylene and R^2 is H, then R^1 is not



;

(e) when A is C_4 alkylene, Y is carbonyl, W is a direct link and R^2 is 3-hydroxy phenyl,

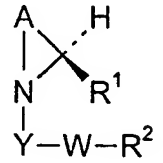
then R^1 is not



; and

(f) when A is C_3 alkylene, Y is carbonyl, W is a direct link and R^2 is phenyl, then R^1 is not furan-2yl.

2. A compound as claimed in claim 1 having the stereochemical formula (I')



(I')

wherein R^1, R^2, A, W and Y are as defined in claim 1 formula (I).

3. A compound as claimed in claims 1 or 2 wherein R^1 is triazolyl, isoxazolyl, oxadiazolyl, tetraazolyl, thiazolyl or thiadiazolyl, that is linked to the adjacent carbon atom by a ring carbon atom and optionally substituted by 1, 2 or 3 substituents each independently selected from C_1-C_6 alkyl, -X-aryl, -X-het, -X-CO_2R^5 and -X-NR^3R^4.

4. A compound as claimed in claim 3 wherein X is a direct link, C_1-C_6 alkylene or -(C_0-C_6 alkylene)-Z-(C_0-C_6 alkylene)-; Z is O, -$CR^5NR^3R^4$, -$CR^5NR^5(CO_2R^5)$-, -NR^5- or -NR^5CO_2-;

wherein said aryl of -X-aryl is phenyl optionally substituted by from 1 to 3 substituents each independently selected from -(C_1-C_6 alkylene)OH,-(C_1-C_6 alkylene)NR^3R^4, -O-(C_1-C_6 alkylene)NR^3R^4 and -(C_1-C_6 alkylene)(phthalimido); and said "het" of -X-het is piperidyl, pyrazinyl, furyl, piperazinyl, pyrimidinyl or morpholinyl, optionally substituted by from 1 to 3 -(C_1-C_6 alkylene)(C_3-C_7 cycloalkyl),-(C_1-C_6 alkylene)aryl substituents; or CO_2R^5 where R^5 is (C_1-C_6 alkylene) aryl; or (C_1-C_6) alkyl; or (C_1-C_6 alkylene) NR^3R^4 where "het" is furyl

R^3 and R^4 are either each independently selected from H and C_1-C_6 alkyl or, when taken together, represent unbranched C_3-C_6 alkylene; and

R^5 is H or C_1-C_6 alkyl.

5. A compound as claimed in any one of the preceding claims wherein R^1 is 1,2,4-

triazolyl, isoxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl or 1,3,4-thiadiazolyl, that is linked to the adjacent carbon atom by a ring carbon atom and optionally

substituted by 1, 2 or 3 substituents each independently selected from methyl, benzyl, α-(amino)benzyl, R or S-∝-(amino)benzyl, α-(tert-butoxycarbonylamino)benzyl, benzylamino, benzylaminoethyl, aminomethylphenoxymethyl, methylaminomethylphenoxymethyl, dimethylaminomethylphenoxymethyl, amino methylphenoxymethyl, hydroxymethylphenoxymethyl, benzylaminoethyl, butoxycarbonylethypiperazinyl, benzoaminomethyl, pyrrolidinylmethylphenoxymethyl, aminoethoxybenzyl, pyrazinyl, cyclopropylmethylpiperidyloxymethyl, hydroxymethylphenoxymethyl, tertbutyloxycarbonylpiperazinylethyl, pyrimidinyl, (S)-α-(benzyloxycarbonylamino)benzyl, piperazinoethyl, phenylcarbonylaminoethyl, dimethylaminoethyl, hydrogen, phenyl, phenethyl, cyclohexylamino phthalimidomethylphenoxymethyl, piperidyloxymethyl, benzylpiperidyloxymethyl, benzylpiperidyloxyethyl, morpholinomethyl, benzyloxycarbonylaminoethyl, amino, aminoethyl, benzyloxycarbonylpiperidinyloxymethyl, methylaminofuranyl or (R)-α-(benzyloxycarbonylamino)benzyl.

6. A compound as claimed in claims 4 or 5 wherein R_1 is
5-benzyl-1,2,4-oxadiazol-3-yl,
5-(4-[phthalimidomethyl]phenoxymethyl)-1,2,4-oxadiazol-3-yl,
5-(4-aminomethylphenoxymethyl)-1,2,4-oxadiazol-3-yl,
5-(4-dimethylaminomethylphenoxymethyl)-1,2,4-oxadiazol-3-yl,
5-(4-pyrrolidinomethylphenoxymethyl)-1,2,4-oxadiazol-3-yl,
5-(4-methylaminomethylphenoxymethyl)-1,2,4-oxadiazol-3-yl,
5-(1-benzylpiperid-4-yloxymethyl)-1,2,4-oxadiazol-3-yl,
5-(α-[tert-butoxycarbonylamino]benzyl)-1,2,4-oxadiazol-3-yl,
5-morpholinomethyl-1,2,4-oxadiazol-3-yl,

5-(2-[1-benzylpiperid-4-yloxy]ethyl)-1,2,4-oxadiazol-3-yl,

5-(1H-piperid-4-yloxymethyl)-1,2,4-oxadiazol-3-yl,

5-[α-[amino]benzyl)-1,2,4-oxadiazol-3-yl,

5-(2-[benzyloxycarbonylamino]ethyl)-1,2,4-oxadiazol-3-yl,

5-(2-aminoethyl)-1,2,4-oxadiazol-3-yl,

5-(2-[benzylamino]ethyl)-1,2,4-oxadiazol-3-yl,

5-(4-[2-aminoethoxy]benzyl)-1,2,4-oxadiazol-3-yl,

5-methyl-1,3,4-thiadiazol-2-yl,

1H-1,2,4-triazol-3-yl,

1-benzyl-1H-1,2,4-triazol-3-yl,

5-benzyl-4-methyl-4H-1,2,4-triazol-3-yl,

5-amino-1,3,4-oxadiazol-2-yl,

5-benzylamino-1,3,4-oxadiazol-2-yl,

3-methylisoxazol-5-yl,

5-(pyrazin-2-yl)-1,2,4-oxodiazol-3-yl,

5-(R)-[α-(amino)benzyl]-1,2,4-oxadiazol-3-yl,

5-(S)-[α-(amino)benzyl]-1,2,4-oxadiazol-3-yl,

5-(5-methylaminofuran-2-yl)-1,2,4-oxadiazol-3-yl,

5-(1-benzyloxycarbonylpiperid-4-yloxymethyl)-1,2,4-oxadiazol-3-yl,

5-(1-cyclopropylmethylpiperid-4-yloxymethyl) -1,2,4-oxadiazol-3-yl,

5-(4-hydroxymethylphenoxymethyl) -1,2,4-oxadiazol-3-yl,

5-[2-(4-tert-butoxycarbonylpiperazin-4-yl)ethyl] -1,2,4-oxadiazol-3-yl,

5-(pyrimidin-2-yl) -1,2,4-oxadiazol-3-yl,

5-methyl-1,2,4-oxadiazol-3-yl,

5-benzylaminomethyl-1,2,4-oxadiazol-3-yl,

5-(S)-(α-[benzyloxycarbonylamino]benzyl) -1,2,4-oxadiazol-3-yl,

5-(R)-(α-[benzyloxycarbonylamino]benzyl) -1,2,4-oxadiazol-3-yl,

5-[2-(4H-piperazin-1-yl)ethyl] -1,2,4-oxadiazol-3-yl,

5-[2-(phenylcarbonylamino)ethyl] -1,2,4-oxadiazol-3-yl,

5-[2-(dimethylamino)ethyl] -1,2,4-oxadiazol-3-yl,

1,2,4-oxadiazol-3-yl,

5-phenyl -1,2,4-oxadiazol-3-yl,

2-benzyl-2H -1,2,3,4-tetraazol-5-yl,
5-benzyl-1,3,4-oxadiazol-2-yl,
5-[2-(phenyl)ethyl] -1,3,4-oxadiazol-2-yl,
5-methyl-2H-1,2,3,4-tetraazol-5-yl,
5-cyclohexylamino -1,3,4-oxadiazol-2-yl,
5-methyl -1,3,4-oxadiazol-2-yl,
3-methyl -1,2,4-oxadiazol-3-yl,
5-methyl -1,3-thiazol-2-yl,
5-methyl-1H- 1,2,4-triazol-3-yl,
5-aminomethyl -1,2,4-oxadiazol-3-yl or
2H- 1,2,3,4-tetraazol-5-yl.

7. A compound according to any one of the preceding claims wherein R^1 is 1,2,4 or 1,3,4 oxadiazole, that is linked to the adjacent carbon atom by a ring carbon atom which is optionally preferably-mono-substituted by one of -X-aryl or -X-het wherein X is preferably selected from -(C_0-C_2 alkylene)-Z-(C_0-C_2 alkylene), more preferably -(C_1 alkylene)-Z-(C_0 alkylene) where Z is -O-; or X is a direct link or -(C_1-C_2 alkylene); or X is -(C_0 alkylene)-Z-(C_0 alkylene) where Z is $-CR^5NR^3R^4$, or $-CR^5 NR^5 (CO_2R^5)$ where R^3 and R^4 are selected from H,-(C_1-C_3 alkylene), more preferably H,-(C_1-C_2 alkylene) and R^5 is H or -(C_1-C_4 alkylene), or -(C_1-C_2 alkylene)aryl; or X is -(C_1-C_2 alkylene) -Z-(C_1-C_2 alkylene)(aryl) where Z is NR^5 and R^5 is H or -(C_1-C_2 alkylene)-;

wherein aryl of -X-aryl is phenyl optionally substituted by from 1 to 3 susbtituents independently selected from -(C_1-C_3 alkylene) NR^3 R^4, -(C_1-C_6 alkylene)(phthalimido); -O(C_1-C_3 alkylene) NR^3 R^4 or $-CO_2R^5$ wherein R^3 and R^4 are each independently selected from H, C_1-C_3 alkyl or, when taken together, represent unbranched C_3-C_5 alkylene; and R^5 is H, C_1-C_4 alkyl or -(C_1-C_2 alkylene) aryl;

wherein "het" of -X-het is piperidinyl, furyl, pyrazinyl, pyrimidinyl or piperazinyl optionally substituted by -(C_1-C_3 alkylene)(-C_3-C_6 cycloalkyl), -$C0_2R^5$, -(C_1-C_3

alkylene)NR_3R_4 or -(C_1-C_2 alkylene)aryl wherein aryl is phenyl and wherein R^3 and R^4 are selected from H,-(C_1-C_3 alkylene), more preferably H,-(C_1-C_2 alkylene) and R^5 is H or -(C_1-C_4 alkylene), or -(C_1-C_2 alkylene)aryl;

or X is -(C_1-C_2 alkylene) -Z-(C_1-C_2 alkylene)(aryl) where Z is NR^5 and R^5 is H or -(C_1-C_2 alkylene)-.

8. A compound as claimed in any one of the preceding claims wherein R^2 is H, phenyl or C_3-C_7 cycloalkyl, said phenyl or cycloalkyl being optionally substituted by from 1 to 3 halo substituents, or R^2 is a 5- or 6- membered ring heterocyclic group containing either 1 or 2 nitrogen heteroatoms or 1 oxygen heteroatom, said heterocyclic group being saturated or partially or fully unsaturated, optionally benzo-fused and optionally substituted, including in the benzo-fused portion, by from 1 to 3 halo, halo(C_1-C_6 alkyl), C1-C_6 alkyl substituents, said R^2 group being attached to W by any mono- or bicyclic ring carbon atom or heteroatom.

9. A compound as claimed in claim 8 wherein R^2 is H, phenyl, cyclopentyl cyclohexyl or cycloheptyl, said phenyl being optionally substituted by from 1 to 3 fluoro substituents, or R^2 is imidazolyl, pyrrolidinyl, piperidinyl or tetrahydrofuranyl, said imidazolyl or tetrahydrofuranyl group being optionally benzo-fused and optionally substituted, including in the benzo-fused portion, by from 1 to 3 methyl, bromine or fluorine substituents, said R^2 group being attached to W by any mono- or bicyclic ring carbon atom.

10. A compound as claimed in claim 9 wherein R^2 is H, fluorophenyl, cyclopentyl, cyclohexyl, cycloheptyl, methylimidazolyl, benzimidazolyl, bromobenzimidazolyl or furanyl,

11. A compound as claimed in claim 10 wherein R^2 is H, 4-fluorophenyl, cyclopentyl, cyclohexyl, cycloheptyl, 1-methyl-1H-imidazol-4-yl, 1H-benzo[d]imidazol-2-yl, 5-bromo-1H-benzo[d]imidazol-2-yl or

tetrahydrofuran-3-yl,

12. A compound as claimed in any one of the preceding claims wherein W is a direct link, methylene, ethylene or 2,2-dimethyl-1,3-propylene.

13. A compound as claimed in any one of the preceding claims wherein Y is SO_2 or -$CONR^5$-., and wherein R^5 is as defined in any one of the preceding claims.

14. A compound as claimed in claim 13 wherein Y is SO_2 or -CONH-.

15. A compound as claimed in any one of the preceding claims wherein -Y-W-R^2 are

5-bromo-1H-benzo[d]imidazolll-2-yl sulphonyl,
1H-benzo[d]imidazol-2-ylsulphonyl,
1-methyl-1H-imidazol-4-ylsulphonyl,
tetrahydrofuran-3-ylmethylsulphonyl,
cyclohexylmethylsulphonyl,
4-fluorophenylsulphonyl,
N-(2,2-dimethylprop-1-yl)aminocarbonyl,
cyclopentylmethylsulphonyl,
cycloheptylmethylsulphonyl,
1-(benzyloxycarbonyl)pyrrolidin-3-ylmethylsulphonyl,
1-(benzyloxycarbonyl)piperid-3-ylmethylsulphonyl,
benzylaminocarbonyl or
phenethylaminocarbonyl.

16. A compound as claimed in any one of the preceding claims selected from the group consisting of:

1*H*-Benzo[d]imidzol-2-yl[2S]-2-(5-benzyl-1,2,4-oxadiazol-3-yl)-1-piperidylsulphone,

2-[4-(3-[(2*S*)-1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzyl]-1,3-isoindolinedione,

4-(3-[(2*S*)-1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzylamine,

N-[4-(3-[(2*S*)-1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzyl]-*N*,*N*-dimethylamine,

3-[1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-5-[4-(1-pyrrolidylmethyl)phenoxy]methyl-1,2,4-oxadiazole,

N-[4-(3-[1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)benzyl]-*N*-methylamine,

4-[3-((2S)-1-[Cyclohexylmethylsulfonyl]-2-piperidyl)-1,2,4-oxadiazol-5-ylmethoxy]benzylamine,

5-[(1-Benzyl-4-piperidyl)oxymethyl]-3-[(2*S*)-1-cyclohexylmethylsulfonyl-2-piperidyl]-1,2,4-oxadiazole,

3-[(2*S*)-1-Cyclohexylmethylsulfonyl-2-piperidyl]-5-[4-piperidyloxymethyl]-1,2,4-oxadiazole,

(3-[(2*S*)-1-Cyclohexylmethylsulfonyl-2-piperidyl]-1,2,4-oxadiazol-5-yl)(phenyl)methylamine,

5-(3-(2*S*)-1-[(Cyclohexylmethyl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)-2-furyl]methylamine,

N-(2-(3-[1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-yl)ethyl)benzylamine,

2-[4-(3-[1-(1*H*-Benzo[*d*]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethyl)phenoxy]ethylamine,

N-(3-[1-(1*H*-benzo[d]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethyl)-*N*-benzylamine,

2-[(2*S*)-2-5-[(4-Piperidyloxy)methyl]-1,2,4-oxadiazol-3-yl-1-piperidyl]sulfonyl-1*H*-benzo[d]imidazole,

2-[(2*S*)-2-[5-([1-(Cyclopropylmethyl)-4-piperidyl]oxymethyl)-1,2,4-oxadiazol-3-yl]-1-piperidyl]sulfonyl-1*H*-benzo[d]imidazole,

2-[(2*S*)-2-(5-Benzyl-1,2,4-oxadiazol-3-yl)-1-piperidyl]sulfonyl-5-bromo-1*H*-benzo[d]imidazole,

2-4-[(3-(2*S*)-1-[(5-Bromo-1*H*-benzo[d]imidazol-2-yl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)methoxy]benzyl-1,3-isoindolinedione,

4-[(3-(2*S*)-1-[(5-Bromo-1*H*-benzo[d]imidazol-2-yl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)methoxy]benzylamine,

tert-Butyl 4-[2-(3-(1*S*)-2-[(cyclohexylmethyl)sulfonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)ethyl]-1-piperazinecarboxylate,

(*R*)-(3-{(2*S*)-1-[(Cyclohexylmethyl)sulfonyl]-2-piperidyl}-1,2,4-oxadiazol-5-yl)(phenyl)methylamine,

(*S*)-(3-{(2*S*)-1-[(Cyclohexylmethyl)sulfonyl]-2-piperidyl}-1,2,4-oxadiazol-5-yl)(phenyl)methylamine,

2-({2-[5-(2-pyrimidinyl)-1,2,4-oxadiazol-3-yl]-2-piperidyl}sulfonyl)-1*H*-benzo[d]imidazole,

Benzyl 4-(3-[(2*S*)-1-(1*H*-benzo[d]imidazol-2-ylsulfonyl)-2-piperidyl]-1,2,4-oxadiazol-5-ylmethoxy)-1-piperidinecarboxylate,

(2S)-2-(5-Benzyl-1,2,4-oxadiazol-3-yl)-1-[(cyclopentylmethyl)sulphonylpiperidine,

(2S)-2-(5-Benzyl-1,2,4-oxadiazol-3-yl)-1-[(cyclohexylmethyl)sulphonylpiperidine,

(2S)-2-(5-Benzyl-1,2,4-oxadiazol-3-yl)-1-[(cycloheptylmethyl)sulphonylpiperidine,

tert-Butyl-N-(3-{(2S)-1-(cyclohexylmethyl)sulphonyl-2-piperidyl}-1,2,4-oxadiazol 5-yl)(phenyl)methylcarbamate,

(2S)-2-(5-{2-[(1-Benzyl-4-piperidyl)oxy]ethyl}-1,2,4-oxadiazol-3-yl)-1-[(cyclohexylmethyl)sulphonyl]piperidine,

{4-{3-{2S-1-[4-Fluorophenyl)sulphonyl]piperidyl}-1,2,4-oxadiazol-5-yl)methoxy]phenyll}methanol,

2-(3-{(2S)-1-[4-Fluorophenyl)sulphonyl]piperidyl}-1,2,4-oxadiazol-5-yl)pyrazine or 1-[2-(3-(1S)-2-[(Cyclohexylmethyl)sulphonyl]-2-piperidyl-1,2,4-oxadiazol-5-yl)ethyl]piperazine.

17. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 16 or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient, diluent or carrier;

18. A compound as claimed in any one of claims 1 to 16 or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a medicament.

19. The use of a compound as claimed in any one of claims 1 to 16 or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment or prophylaxis of neuronal degeneration.

20. The use of a compound as claimed in any one of claims 1 to 16 or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the promotion of neuronal regeneration and outgrowth.

21. The use of a compound as claimed in any one of claims 1 to 16 or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of a neurological disease or disorder selected from the group consisting of senile dementia (Alzheimer's disease) and other dementias, amyotrophic lateral sclerosis and other forms of motor neuron disease, Parkinson's disease, Huntington's disease, neurological deficits associated with stroke, all forms of degenerative disease affecting the central or peripheral nervous system (e.g. cerebellar-brainstem atrophies, syndromes of progressive ataxias), all forms of muscular dystrophy, progressive muscular atrophies, progressive bulbar muscular atrophy, physical or traumatic damage to the central or peripheral nervous system (e.g. spinal cord), herniated, ruptured or prolapsed intervertebrae disc syndromes, cervical spondylosis, plexus disorders, thoracic outlet syndromes, all forms of

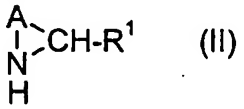
peripheral neuropathy (both diabetic and non-diabetic), trigeminal neuralgia, glossopharyngeal neuralgia, Bell's Palsy, all forms of auto-immune related disease resulting in damage of the central or peripheral nervous system (e.g. multiple sclerosis, myasthenia gravis, Guillain-Barré syndrome), AIDS related disorders of the nervous system, dapsone ticks, bulbar and retrobulbar affections of the optic nerve (e.g. retinopathies and retrobulbar neuritis), hearing disorders such as tinnitus, and prion diseases.

22. Use as claimed in claim 20 where the neurological disease or disorder is senile dementia (Alzheimer's disease) or another dementia, amyotrophic lateral sclerosis or another form of motor neuron disease, Parkinson's disease, Huntington's disease, a neurological deficit associated with stroke, physical or traumatic damage to the central or peripheral nervous system (e.g. spinal cord), a peripheral neuropathy (either diabetic or non-diabetic), multiple sclerosis or a hearing disorder such as tinnitus;

23. A method of treatment of a human to treat neuronal degeneration which comprises treating said human with an effective amount of a compound as claimed in any one of claims 1 to 16 or with a pharmaceutically acceptable salt, solvate or composition thereof.

24. A process for the preparation of a compound of formula (I) comprising:

(a) reaction of a compound of the formula:



(II)

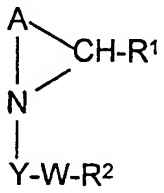
wherein R^1 and A are as defined in claim 1 for a compound of formula (I), with a compound of the formula (III):

$$L^1\text{-}Y\text{-}W\text{-}R^2 \qquad (III)$$

wherein R^2, W and Y are as previously defined in claim 1 for a compound of the formula (I) and L^1 is a suitable leaving group; or

(b) by ring formation of R^1 or ring closure of a corresponding open ring structure of R^1, in formula (II) wherein A is as defined in claim 1 for a compound of formula (I), and wherein the said open ring corresponds to an optionally substituted heterocycle R^1, as is defined in claim 1 for a compound of formula (I), followed by reaction with a compound of formula (III); or

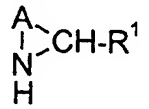
(c) by ring formation of R^1 or ring closure of a corresponding open ring structure of R^1, in formula (I):



(I)

wherein A is as defined in claim 1 for a compound of formula (I), and wherein the said open ring corresponds to an optionally substituted heterocycle R^1, as is defined in claim 1.

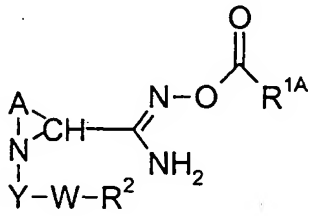
25. A compound having the general formula (II):



(II)

wherein R^1 and A are as defined in claim 1 for a compound of formula (I).

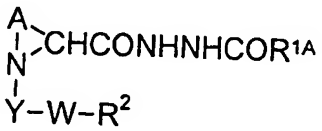
26. A compound of general formula (XIIA):



(XIIA)

wherein R^2, A, W and Y are as previously defined for a compound of the formula (I) and R^{1A} is a relevant group corresponding to an optional substituent on the heteroaryl group as previously defined for R^1 for a compound of the formula (I).

27. A compound of general formula (XIV):



(XIV)

wherein R^2, A, W and Y are as previously defined for a compound of the formula (I) and R^{1A} is a relevant group corresponding to an optional substituent on the heteroaryl group as previously defined for R^1 for a compound of the formula (I).

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/IB 99/00259

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D413/14 C07D413/04 C07D417/04 C07D401/04 A61K31/445
C07D211/60 C07D207/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KIYOOKA, SYUN-ICHI ET AL: "A short synthesis of a pyrrole derivative having a chiral substituent" SYNTHESIS (1988), (9), 745-6,1988, XP002074252 * page 746, "reference" 4 * ---	1
X	WO 97 03973 A (FUJISAWA PHARMACEUTICAL CO ;TANIGUCHI KIYOSHI (JP); HATTORI KOUJI) 6 February 1997 see preparation 67 see claim 10 ---	1
A	WO 96 40633 A (GUILFORD PHARM INC) 19 December 1996 cited in the application see abstract; claim 1 ---	1,17-23
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 April 1999	10/06/1999

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/IB 99/00259

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE Beilstein BRN=121325, XP002100247 & VECCHIETTI: JOURNAL OF MEDICINAL CHEMISTRY., vol. 34, no. 1, 1991, pages 397-403, WASHINGTON US ---	25
X	DATABASE CROSSFIRE Beilstein BRN=5814911, XP002100251 & STOLLE: JOURNAL OF ORGANIC CHEMISTRY., vol. 57, no. 11, 1992, pages 3000-3007, EASTON US ---	25
X	DATABASE CROSSFIRE Beilstein BRN=6922736, XP002100252 & MAHBOOBI: ARCH. PHARM., vol. 327, no. 7, 1994, pages 417-428, ---	25
X	DATABASE CROSSFIRE Beilstein BRN=958008, XP002100253 & PROKAI-TATRAI: TETRAHEDRON., vol. 50, no. 33, 1994, pages 9909-9918, OXFORD GB ---	25
X	DATABASE CROSSFIRE Beilstein BRN=82637, XP002100254 & SADYKOW: ZH. OBSHCH. KHIM., vol. 17, 1947, page 1212 ---	25
X	DATABASE CROSSFIRE Beilstein BRN=81965, XP002100255 & ALBERICI: TETRAHEDRON LETTERS., vol. 24, no. 18, 1983, pages 1937-1940, OXFORD GB ---	25
X	DATABASE CROSSFIRE Beilstein BRN=7587535, XP002100256 & WANNER: JOURNAL OF ORGANIC CHEMISTRY., vol. 61, no. 16, 1996, pages 5581-5586, EASTON US --- -/--	25

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INTERNATIONAL SEARCH REPORT

Interr ıal Application No
PCT/IB 99/00259

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE Beilstein BRN=5012306, XP002100257 & TOKUYAMA: TETRAHEDRON., vol. 39, no. 1, 1983, pages 41-47, OXFORD GB -----	25

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